

REVIEW OF LITERATURE ON CLINICAL PANCREATOLOGY

Scientific literature made available

Selected and edited by

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REVIEWER'S PREFACE (and search algorithm)

This is a compilation of the reports of the three first quarters of 2010 on what is written in the scientific literature on pancreas. The main source has been PubMed, but also the Journals *Pancreas*, *Pancreatology* and *Journal of the Pancreas* has been scrutinized. Only full papers are included, and almost all languages have been accepted (Karolinska Insitutet in Stockholm is a truly international institution, and I thank all the friends with other mother touns than my own who has helped me). Not *all* articles are included, but the collection is not far from completeness – some articles, however, were too superficial or too poor in other ways, so in my own right I omitted them.

The MeSHs used were *pancreas*, *pancreatic cancer*, *acute pancreatitis*, *chronic pancreatitis*, *pancreatic pseudocysts*, and *pancreatic trauma*. Exlusion criteria were *not-human*. Besides, physiology, diabetes, endocrine tumors and transplantation have been included only in a few cases when the reviewer could not resist. Of course there is a lot of important knowledge also in these fields and in experimental work with cells, cell-lines, and whole animals, but my brain and my time is not sufficient to make a complete work-up on this – I leave it to somebody with a better brain or more time, or both.

Regarding the limitations, first of all only some of the articles have been read in their full length, and the writing is therefore based on their abstracts for practical reasons. This is also in line with the aim of the review: not to report all what has been published, but rather to give an introductional sample that hopefully will make the reader eager to read the whole article or articles: “a tast of clinical pancreatology in 2010”. Also, I make very little judgement of the quality of what has been written – I hope the reader will do a more thorough quality control later on regarding the articles they are really interested in.

The reson for collecting the articles are purely personal: I want to know what is happening in clinical pancreatology. If I only try to read the new articles unfortunately my memory is too elusive andf my mind has a tendency to fly to other interesting thoughts (patients, family, music, football etc), but if I have to handle the text I remember at least the conclusions a little bit better. My best way of both understanding and remember is to write things down (the computer's brain is less emotional and less prone to be tired than mine). After I then have collected and organized the texts I can just as well let other use it – if they are interested.

The plan is to follow these quarters by a new review next quarter and next quarter and so on (it is then the quarter when the review was made available through PubMed that counts, not the month it was actually published). All quarters are then merged into an “encyclopedia”. So, welcome with comments – and if the comments fail to appear, the next quarters and years will probably have the same disposition, advantages and failures as the present. Welcome back next quarter!

I like to write these reviews, if you can use them in one way or another we might both be happy!

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REVIEWER'S PREFACE (and search algorithm)

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REFERENCES

ABBREVIATIONS

AAL	Aleuria aurantia lectin
ABP	acute biliary pancreatitis
AC	adenocarcinomas
ACC	acinar cell carcinoma
aCEC	activated circulating endothelial cells
ACEI	angiotensin I-converting enzyme inhibitor
Ach	acetylcholine
Ach3	acetylated histone H3
ACOSOG	American College of Surgeons Oncology Group
ACP	alcoholic chronic pancreatitis
ACP	anaplastic carcinoma of the pancreas
ACS	abdominal compartment syndrome
ADM	acinar-ductal metaplasia
ALB	albumin
ALC	absolute lymphocyte counts
AIP	autoimmune pancreatitis
ALCAM	activated leukocyte cell adhesion molecule
ANA	antinuclear antibody
Angio	angiopoietin
ANP	acute necrotizing pancreatitis
AOR	adjusted odds ratio
AP	acute pancreatitis
AP	annular pancreas
APACHE	Acute Physiology and Chronic Health Examination
APC	advanced pancreatic carcinoma
APC	activated protein C
APICS	Autoimmune Pancreatitis International Cooperative Study Group
AR	arterial resection
AR	augmented reality
ARB	angiotensin II type-1 receptor blocker
ARP	acute recurrent pancreatitis
aRR	adjusted relative risk
ASA	American Society of Anesthesiologists
ASC	adenosquamous carcinoma
ACS	abdominal compartment syndrome
ASCO	American Society of Clinical Oncology
ASIR	adaptive statistical iterative reconstruction
AUC	area under the curve
BCC	basal cell skin cancer
BD-IPMN	branch ducts intraductal papillary mucinous neoplasm
BiIIN	biliary intraepithelial neoplasia
BISAP	bedside index for severity in acute pancreatitis
BDL	bile duct ligation
B2M	and beta-2-microglobulin
BMI	body mass index
BPH	benign prostatic hyperplasia
BPT	benign pancreatic tumor
BTC	biliary tract cancer
CA	celiac axis
CA	carbohydrate antigen
Ca	calcium

CA 19-9	carbohydrate antigen 19-9
CaG	chromogranin A
CAN	coefficient of nitrogen absorption
CaSR	calcium-sensing receptor
CA/TD	centroacinar cells and terminal ducts
Cav1	caveolin-1
CBD	common bile duct
CBDS	common bile duct stone
CCD	continuous daily dosing
CCI	Charlson combined comorbidity index
CCE	cholesterol crystal embolization
CCK	cholecystokinin
CCP	calcific chronic pancreatitis
CD	cluster of differentiation
CD	celiac disease
CD	Castleman disease
CDD	continuous daily dosing
CDDP	cisplatin
CEA	carcinoembryonic antigen
CEC	circulating endothelial cells
CECT	contrast-enhanced computerized tomography
CENTRAL	Cochrane Central Register of Controlled Trials
CER	cost-effectiveness ratio
CEUS	contrast-enhanced ultrasound
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFRD	CF-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CgA	chromogranin A
CHA	common hepatic artery
CI	confidence interval
CI	conformity indices
CIS	carcinoma in situ
CLD	clear liquid diet
CLDN	claudin
CNR	contrast-to-noise ratio
CNS	central nervous system
COC	Commission on Cancer
COX-2	cyclooxygenase-2
CP	chronic pancreatitis
CP	central pancreatectomy
CPB	celiac plexus block
CPB1	carboxypeptidase B1
CPEN	cystic pancreatic endocrine neoplasm
CR	complete response
CRAI	continuous regional arterial infusion
CrCl	creatinine clearance
CRC	colorectal cancer
CREB	3'-5'-cyclic adenosine monophosphate response element binding protein
CRP	C-reactive protein
CRT	chemoradiation
CT	computed tomography
CTA	computed tomography angiography
CTSI	computed tomography severity index

CWP	cyst wall puncture
3-D	3-dimensional
DBE	double-balloon enteroscopy
DC	ductal carcinoma
DCE	dynamic contrast-enhanced
DFS	disease-free survival
DGE	delayed gastric emptying
DHT	dihydrotestosterone
DLBCL	diffuse large B-cell lymphoma
DL-PLC	diagnostic laparoscopy and peritoneal lavage for cytology
DLPR	disconnected left pancreatic remnant
DLT	dose-limiting toxicity
DM	diabetes mellitus
DOR	diagnostic odds ratios
DP	distal pancreatectomy
DP-CAR	distal pancreatectomy with celiac axis resection
DPD	dihydropyrimidine dehydrogenase
DPHRP	duodenum-preserving resection of the head of the pancreas
DRG	dorsal root ganglia
DSA	digital subtraction angiography
DSC	differential scanning calorimetric
DSS	disease-specific survival
DVH	dose-volume histogram
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
EBER	Epstein-Barr virus-encoded RNA
EBRT	external beam radiotherapy
EBV	Epstein-Barr virus-encoded RNA
EBV-SMT	Epstein-Barr-associated smooth muscle tumor
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
ECP	endothelial progenitors
EGC	early gastric cancer
EGFR	epidermal growth factor receptor
EHCC	extrahepatic bile duct carcinoma
EID-1	E1A-like inhibitor of differentiation 1
ELC	endothelial lineage cells
ELISA	enzyme-linked immunosorbent assay
EMT	epithelial to mesenchymal transition
EN	enteral nutrition
ENBD	extrahepatic biliary ducts
EndoCAb	antiendotoxin core antibodies
ENT1	equilibrative nucleoside transporter 1
EOSPC	efficacy-orientated sequential palliative chemotherapy
EPC	exocrine pancreatic cancer
EPCR	endothelial cell protein C receptor
ePFT	endoscopic pancreatic function test
EPI	exocrine pancreatic insufficiency
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
ERCC1	excision repair cross complementing 1
ERCP	endoscopic retrograde cholangiopancreatography
ERK	extracellular signal-regulated kinase
ERP	endoscopic retrograde pancreatography
ES	endoscopic sphincterotomy

ES	early surgery
ESPAC	European Study Group for Pancreatic Cancer
ESR	erythrocyte sedimentation rate
ESWL	extracorporeal shock wave lithotripsy
ETS	environmental tobacco smoke
EUS	endoscopic ultrasonography
EUS-FNA	endoscopic ultrasound-guided fine-needle aspiration
FaPaCa	familial pancreatic cancer
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFLP	freedom-from-local-progression
FFQg	Food Frequency Questionnaire Based on Food Groups
FHH	familial hypocalciuric hypercalcemia
5f-IMRT	five-field IMRT intensity-modulated radiotherapy
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
FNAB	fine-needle aspiration biopsy
FNAC	endoscopic ultrasound-guided fine needle aspiration cytology
FOM	figure of merit
FPC	familial pancreatic cancer
FSH	follicle-stimulating hormone
FT	tegafur
FT-IR	fourier transform infrared spectroscopy
FTR	failure to rescue
5-FU	5-fluorouracil
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GCI	glycemic control improvement
GCK	glucokinase
Gd	gadolinium
GDM	gestational diabetes mellitus
GDNF	glial cell-derived neurotrophic factor
GEL	granulocyte epithelial lesion
GEM	gemcitabine
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GFPT	glutamine-fructose-6-phosphate transaminase
GI	gastrointestinal
GIC	gastrointestinal epithelial contamination
GIP	glucose-dependent insulinotropic polypeptide
GIST	gastrointestinal stromal tumor
GLP-2	glucagon-like peptide-2
GNC	gene copy number
GP2	glycoprotein 2 gene
GPC	gel permeation chromatography
GSTA4	glutathione S-transferase alpha 4
GSTM1	glutathione S-transferase M1
GSTT1	glutathione S-transferase theta 1
GTV	gross tumor volume
HAT	anionic trypsinogen
HCT	cationic trypsinogen
HCV	hepatitis C virus
HGF	hepatocyte growth factor
HIFU	high-intensity focused ultrasound
HK2	hexokinase 2
HLA	human leukocyte antigen
hMVEC	human microvascular endothelial cells

HP	hereditary pancreatitis
HP	hyperechogenic pancreas
HP	heterotopic pancreas
HPB	hepatopancreatobiliary
hPSC	human pancreatic stellate cells
HR	hazard ratio
HRM	high-resolution melting
HRQL	health-related quality of life
HT	hypertension
HuR	Hu protein antigen R
HV	healthy volunteers
HVHF	continuous high-volume hemofiltration
IAC	IgG4-associated cholangitis
IAH	intra-abdominal hypertension
IAP	inhibitors of apoptosis proteins
IAP	intra-abdominal pressure
IAP	idiopathic acute pancreatitis
IAPN	intra-ampullary papillary-tubular neoplasm
IAPP	islet amyloid polypeptide
IAT	islet cell autotransplantation
IBD	inflammatory bowel disease
ICC	immunocytochemistry
ICC	intrahepatic cholangiocarcinoma
ICER	incremental cost effectiveness ratio
ICU	intensive care unit
ID	internal drainage
IDCP	idiopathic duct-centric pancreatitis
IDUS	intraductal ultrasonography
I-FABP	intestinal fatty acid binding protein
IFN	interferon
Ig	immunoglobulin
IGF1	insulin-like growth factor 1
IGFBP	insulinlike growth factor binding protein
IgG	immunoglobulin G
IgG4	immunoglobulin G fraction 4
IHC	immunohistochemistry
IHCCC	intrahepatic bile duct carcinoma
IL	interleukin
IL1RAcP	ST2L/IL1 receptor accessory protein
IMRT	intensity-modulated radiotherapy
IOC	intra-operative cholangiography
IORT	intraoperative radiotherapy
IPAS	intrapancreatic accessory spleen
IPDA	inferior pancreatico-duodenal artery
IPG	intraductal polypoid growth
IPMA	intraductal papillary mucinous adenoma
IPMC	intraductal papillary mucinous carcinoma
IPMN	intraductal papillary mucinous neoplasms
IPN	infected pancreatic necrosis
IQR	interquartile range
IR	insulin receptor
IR	ionising radiation
IR	incidence rates
IROX	irinotecan and oxaliplatin
IRS	incidence rates

ISGPS	International Study Group on Pancreatic Surgery
ITPN	Intraductal tubulopapillary neoplasm
IV	intravenously
IVC	inferior vena cava
JPHC	Japan Public Health Center-based Prospective study
JSLE	juvenile systemic lupus erythematosus
KLK3	kallikrein-related peptidase 3
KPS	Karnofsky performance status
LADG	laparoscopy-assisted distal gastrectomy
LAPC	locally advanced pancreatic cancer
LAP/LUS	laparoscopy and laparoscopic ultrasonography
LAR	long acting repeatable
L-ASNase	L-asparaginase
LBC	liquid-based cytologic
LC	laparoscopic cholecystectomy
LC	local control
LCCBDE	laparoscopic common bile duct exploration
LDP	laparoscopic distal pancreatectomy
LEC	pancreatic lymphoepithelial cysts
LMG	life months gained
LNR	lymph node ratio
LODS	logistic organ dysfunction system
LOH	loss of heterozygosity
LPH	lipomatous pseudohypertrophy
LPJ	lateral pancreaticojejunostomy
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LPSP	lymphoplasmacytic sclerosing pancreatitis
LR-LPJ	local head resection with lateral pancreaticojejunostomy
LSP	left-side pancreatectomy
LTA	lipoteichoic acid
LUS	laparoscopic ultrasonography
LVD	lymphatic vessel density
LV5FU2-CDDP	5-fluorouracil, folinic acid and cisplatin combination
MAP	mild acute pancreatitis
MAPK	mitogen-activated protein kinase
MARPAN	minimal access retroperitoneal pancreatic necrosectomy
MBP	mechanical bowel preparations
MCG	multifocal cholesterol granulomas
MCL	mucinous cystic lesions
MCN	mucinous cystic neoplasm
MCP-1	monocyte chemoattractant protein 1
MD	mean difference
MDCT	multidetector computed tomography
MD-IPMN	main pancreatic duct intraductal papillary mucinous neoplasm
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasias
MEN 1	multiple endocrine neoplasia type-1
MePEG	methoxy poly ethylene glycol
MeSpd	methylspermidine
MetS	metabolic syndrome
Mg	magnesium
MHT	menopausal hormonal therapy
MI	mitotic activity index
mid-BP	mid-blood pressure

miR	microRNA
MMC	mitomycin C
MMP	matrix metalloproteinase
MMP-9	matrix metalloprotease 9
MOF	multiorgan failure
MOLPS	multiorgan lymphoproliferative syndrome
MP	middle pancreatectomy
MP	myenteric plexus
MPD	main pancreatic duct
MPO	myeloperoxidase
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRP5	multidrug resistance protein 5
MRS	magnetic resonance spectroscopy
MRSA	methicillin resistant Staphylococcus aureus
MRSI	magnetic resonance severity index
MTB	metabolic tumor burden
MTD	maximum tolerated dose
MUC	mucin
M/V	volume-corrected mitotic index
MVA	multivariate analysis
N0	negative lymph node
NAA	N-acetyl aspartate
NAFLD	nonalcoholic fatty liver disease
NAT2	N-acetyl transferase
NCI	National Cancer Institute
NDLR	negative diagnostic likelihood ratio
NESB	non-English speaking background
NET	neuroendocrine tumor
NG	naso-gastric
NGAL	neutrophil gelatinase-associated lipocalin
NGF	nerve growth factor
NHL	non-Hodgkin's lymphoma
NIS	Nationwide Inpatient Sample
NJ-EN	naso-jejunal enteral nutrition
NK	natural killer
NLR	neutrophil-lymphocyte ratio
NMCL	non-mucinous cystic lesion
NMR	nuclear magnetic resonance
NOTES	natural orifice transluminal endoscopic surgery
NP	normal pancreas
NPV	negative predictive value
NQO1	NADPH-quinone oxidoreductase 1
NS	not significant
NSAID	non-steroidal anti-inflammatory drug
NTCP	normal tissue complication probability
OAR	organs at risk
OBL	operative blood loss
OC	organochlorine compounds
ODC	ordinary ductal carcinoma
ODP	open distal pancreatectomy
OF	organ failure
OFD I	oral-facial-digital syndrome type 1

25(OH)D	25-hydroxyvitamin D
OR	odds ratio
ORR	objective response rate
OS	ovarian stroma
OS	overall survival
OSR1	oxidative stress-responsive kinase 1
OX	oxaliplatin
OxP	oxaliplatin
Oxo	oxonate
PAC	pancreatic adenocarcinoma
PAC	periampullary cancer
PaCa	pancreatic cancer
PAEE	palmitic acid ethyl ester
PAF	pancreatic anastomotic failure
PALK	pancreas after living donor kidney transplant
PanCa	pancreatic cancer
PanIN	pancreatic intraepithelial neoplasia
PAR	population-attributable risk
PB	pancreatoblastoma
PBC	primary biliary cirrhosis
PBC	proximal biliary cancers
PBD	preoperative biliary drainage
PBM	pancreaticobiliary maljunction
PBMC	peripheral blood mononuclear cells
PC	pancreatic carcinoma
PCC	pancreatic cancer cell (lines)
PCFT	proton-coupled folate transporter
PCL	pancreatic cystic lesion
PCL	poly epsilon caprolactone
PCR	polymerase chain reaction
PD	pancreaticoduodenectomy
PD	pancreatic duct
PD	progressive disease
PDA	pancreatic ductal adenocarcinoma
PDC	pancreatic ductal carcinoma
PDCA	pancreatic ductal adenocarcinoma
Pdcd4	programmed cell death 4
PDAC	pancreatic ductal adenocarcinoma
PDG	pancreatic duct glands
PDGF	platelet-derived growth factor
PDLR	positive diagnostic likelihood ratio
PEA	poorly enhanced areas
PEI	pancreatic exocrine insufficiency
PEP	post-ERCP-pancreatitis
PERT	pancreatic-enzyme replacement therapy
PET	positron emission tomography
PET	pancreatic endocrine tumor
PF	pancreatic fistula
PFS	progression-free survival
PFT	pancreatic function test
PG	pancreaticogastrostomy
PGA	polyglycolic acid
PHHI	persistent hyperinsulinemic hypoglycemia of infancy
pHPT	primary hyperparathyroidism
PHRSD	pancreatic head resection with segmental duodenectomy

PJS	Peutz-Jeghers syndrome
PIGF	placental growth factor
PJ	pancreaticojejunostomy
PKD	polycystic kidney disease
PLR	platelet-lymphocyte ratio
PN	parenteral nutrition
PNET	pancreatic neuroendocrine tumors
PNMC	neurotrophic migration of cancer cells
POD	post-operative day
POF	persistent organ failure
POPF	post-operative pancreatic fistula
PPC	pancreatic/perpancreatic cancers
PPL	primary pancreatic lymphoma
PPPD	pylorus-preserving pancreaticoduodenectomy
PPV	positive predictive value
PR	partial response
PR	progesterone receptor
ProCT	procalcitonin
PRSS1	cationic trypsinogen
PRSS2	anionic trypsinogen gene
PRSS3	mesotrypsin
PS	performance status
PS	pancreatic surgery
PS	plastic stent
PS	pancreatic steatosis
PSA	prostate-specific antigen
PSC	pancreatic stellate cells
PSC	primary sclerosing cholangitis
PSTI	pancreatic secretory trypsin inhibitor
PT	pancreas transplantation
PTBD	percutaneous transhepatic biliary drainage
PTFE	polytetrafluoroethylene
PTV	planning target volume
PV	portal vein
PVT	portal vein thrombosis
QOL	quality of life
RA	RapidArc
RAGE	receptor for advanced glycation end products
RAP	recurrent acute pancreatitis
RAS	renin-angiotensin system
RCC	renal cell carcinoma
rCEC	resting circulating endothelial cells
RCT	randomised controlled trials
RF	rheumatoid factor
RF	radio frequency
RFA	radiofrequency ablation
RFC	reduced folate carrier
RFLP	restriction fragment length polymorphism
RII	relative indices of inequality
RLND	regional lymph node dissection
ROC	receiver-operator characteristic
RP-HPLC	reverse phase high performance liquid chromatography
RR	relative risk
RRG	renal rim grade
RSID	relative signal intensity decreases

RSP	right-side pancreatectomy
RT	radiotherapy
rTMS	repetitive transcranial magnetic stimulation
RT-PCR	reverse transcription-polymerase chain reaction
SABP	severe acute biliary pancreatitis
SAP	severe acute pancreatitis
SBRT	stereotactic body radiotherapy
SC	sclerosing cholangitis
SCA	serous cystadenoma
SCID	severe combined immunodeficient
SCN	serous cystic neoplasm
SDS	Shwachman-Diamond syndrome
SDF-1	Stromal cell-derived factor-1
SEER	Surveillance, Epidemiology, and End Results
SEMS	self-expanding metal stents
SES	socioeconomic status
Shh	sonic hedgehog
SII	secondary somatosensory cortex
SIR	standardized incidence ratios
SIRS	systemic inflammatory response syndrome
SL	staging laparoscopy
SM	sclerosing mesenteritis
SMA	superior mesenteric artery
SMA	smooth muscle actin
Smac	second mitochondria-derived activator of caspase
SMCA	serous microcystic adenoma
SMR	standardized mortality ratio
SMV	superior mesenteric vein
SNOMED	systematized nomenclature of medicine
SNP	single-nucleotide polymorphism
SOD	superoxide dismutase
SPAK	SPS1-related proline/alanine-rich kinase
SPC	sporadic pancreatic cancer
SPDP	spleen-preserving distal pancreatectomy
SPINK	serine protease inhibitor Kazal type
SPINK1	serine protease inhibitor Kazal type1
SPKT	simultaneous pancreas-kidney transplantation
SPT	solid pseudopapillary tumor
SROC	summary receiver-operating characteristic
SRS	stereotactic radiosurgery
SRS/SRT	radiosurgery/radiotherapy
SSAT	spermidine/spermine N ¹ -acetyltransferase
SSPPD	subtotal stomach-preserving pancreaticoduodenectomy
SSTR	somatostatin receptors
STAT	signal transducers and activators of transcription
SU	Shore unit
SUV _{max}	maximum standardized uptake value
TAA	tumor-associated antigens
TAE	transcatheter arterial embolization
TAP	transanastomotic pancreatic
TAT-2	tumor-associated trypsinogen-2
TC	total cholesterol
TCM	traditional Chinese medicine and Western medicine
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

TEAE	treatment-emergent adverse events
TFF2	trefoil factor 2
TGF	transforming growth factor
THIN	The Health Improvement Network
TIC	time-signal intensity curve
TKI	tyrosine kinase inhibitor
TM	thrombomodulin
TMA	tissue microarray
TNF	tumor necrosis factor
TNM	tumor-node-metastasis
TP	total pancreatectomy
TPST2	tyrosylprotein sulfotransferase-2
TS	thoracoscopic splanchnicectomy
TS	transduodenal sphincterotomy
TSG	tumor suppressor gene
TTP	time-to-progression
TTF-1	thyroid transcription factor-1
TTHM	total trihalomethanes
Tu-M2-PK	tumor M2 pyruvate kinase
UrBT	uracil breath test
UC	ulcerative colitis
US	ultrasonography
UTDT	urinary trypsinogen-2 dipstick test
UVB	ultraviolet B
VAcHT	ACh transporter
VAS	visual analog scale
VAT	visceral adipose tissue
VDPP	vitamin D pooling project
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau disease
VIP	vasoactive intestinal peptide
VR	virtual reality
VREP	very rare exocrine neoplasms of the pancreas
VTE	venous thromboembolism
WDNET	well-differentiated neuroendocrine tumor
WM	western medicine
WOPN	walled-off pancreatic necrosis
ZES	Zollinger-Ellison syndrome

PANCREATIC MEDICAL HISTORY

German contributions

Throughout much of history, surgery of the pancreas was restricted to drainage of abscesses and treatment of traumatic wounds. At the turn of the 20th century under the impetus of anesthesia, such surgical stalwarts as Mayo Robson, von Micklewitz, and Sir Moynihan began to deploy laparotomy and gauze drainage in an effort to salvage patients afflicted with severe acute pancreatitis. After the routine use of ether narcosis and surgical antisepsis, the evolution of surgery experienced fascinating and genuinely surgical technique-related advancements. Surgeons from Germany contributed strongly to the upturn of operative treatment in the second half of the nineteenth century. B von Langenbeck inaugurated in 1852 an osteosynthese device in a patient with pseudoarthrosis and opened up surgery also for softer areas. He is credited to be the very first in introducing the principle of *fixateur externe*. Theodor Billroth performed in 1873 the first extirpation of the larynx in a patient with a malignant tumor. Postoperatively, the patient was cared with an artificial larynx. The first successful resection of the distal stomach was also inaugurated by Billroth, in 1881, and was later called the Billroth II procedure. Rydygier from Kulm and Billroth from Wien are the first who successfully performed resection of the lower part of the stomach with anastomosis to the duodenum (Billroth I type of resection). In 1883, Theodor Kocher from Bern reported 101 cases of thyroidectomy, the largest single-surgeon experience. L. Rehn from Frankfurt did in 1887 the first successful suturing of a beating heart to repair a large stab wound. A. Braun, Königsberg, presented in 1892 his techniques of side-to-side anastomosis of the intestine to avoid a circular intestinal anastomosis. F. Sauerbruch from Breslau published in 1904 his thoracotomy chamber with space for two surgeons opening routine access to intrathoracic tissues protecting pulmonary ventilation during surgery. Walter Kausch from Berlin reported in 1912 about three successful pancreatic head resections for peripapillary cancer. The first successful pancreatic head resection was performed in 1909 in a patient with a cancer of the papilla. The patient survived for a long term [001].

Over the next thirty years, surgical intervention in severe pancreatitis became the therapy for choice, despite surgical mortality rates that often exceeded 50 percent. When the discovery of the serum test for amylase revealed that clinically milder forms of acute pancreatitis existed that could respond to nonoperative therapy, a wave of conservatism emerged. For the next quarter century, surgical intervention for severe acute pancreatitis was rarely practiced. However, by the 1960s, conservative mortality rates for severe pancreatitis were reported to be as high as 60 to 80 percent, leading surgeons to not only refine the indications for surgery in severe acute pancreatitis, but also to consider new approaches. Extensive pancreatic resections for severe pancreatitis became the vogue in continental surgical centers in the 1960s and 1970s, but often resulted in high mortality rates and inadvertent removal of viable tissue. Accurate diagnosis of pancreatic necrosis by dynamic CT led to new approaches for management. Some surgeons recommended restricting intervention to those with documented infected necrosis, and proposed delayed exploration employing sequestrectomy and open-packing. Others advocated debridement early in the course of the disease for all patients with necrotizing pancreatitis, regardless of the status of infection. In the 1990s, however, a series of prospective studies emerged proving that nonoperative management of patients with sterile pancreatic necrosis was superior to surgical intervention, and that delayed intervention provided improved surgical mortality rates. The surgical odyssey in managing the necrotizing form of severe acute pancreatitis, from simple drainage, to resection, to debridement, to sequestrectomy, although somewhat tortuous, is nevertheless a notable example of how evidence-based knowledge leads to improvement in patient care. Today's 10 to 20 percent surgical mortality rates reflect not only considerable advances in surgical management, but also highlight concomitant improvements in fluid

therapy, antibiotics, and intensive care. Although history documents the important contributions that surgical practitioners have made to acute pancreatitis and its complications, surgeons are rarely complacent, and the recent emergence of minimally invasive techniques holds future promise for patients afflicted with this "... most formidable of catastrophes" [002].

Acute pancreatitis in the 20th century

The treatment of acute pancreatitis is based in decades long past but still have impact on the therapy of this disease today. The history identifies in retrospect the correct avenues of research and the blind alleys, and describes the ebb and flow of interest in various forms of management. Acquaintance with the work of previous investigators [003-005] may prevent the unnecessary rediscovery of old principles of treatment.

Principle of minimizing toxicity

It was clear from the outset that acute pancreatitis can be divided into the relatively harmless edematous or interstitial form and the initially often fatal necrotizing form. The necroses were thought to have a toxic effect on the course of the disease. However, the diagnosis of acute pancreatitis was very difficult. In the absence of laboratory tests and imaging procedures, clinical examination was crucial. Diagnostic pointers were a history of biliary colic, obesity, occurrence of the first symptoms after consumption of a large meal, severe cyanosis, and possibly hematemesis. Acute pancreatic necrosis was confirmed by the presence of initial shock [006], so the diagnosis became clear only late in the disease course. Once acute necrotizing pancreatitis had been diagnosed with the aid of the few means at hand, it was considered absolutely necessary to operate immediately and remove the necroses. The surgical treatment initially comprised opening the abdominal cavity to drain off an exudate [007]; it was only later that surgical interventions were performed on the pancreas itself.

One of the first to recommend surgical intervention for pancreatitis was the Chicago surgeon Nicholas Senn [008] cited by Rocha et al [009]. At that time, in the 1880s, pancreatitis was believed to be the response of the pancreas to duodenal disease. Senn recommended drainage and removal of all necrotic tissue. In what was probably the largest study of the time, Schmieden and Sebenig [010] reported on 1,278 patients with acute pancreatitis, of whom 654 died, representing a mortality of 51 percent. The authors recommended operation over observation, but described the pancreas as an organ inimical to surgery. Right up to the 1940s, the main cause of death in acute pancreatitis was circulatory shock, undoubtedly a consequence of ignorance of the modern principles of intensive care medicine [011]. Even then, however, some voices warned against operating unnecessarily [012]. Morton [013] found that patients with interstitial pancreatitis, then known as "acute pancreatic edema", were best left in peace. If operated upon, 27 percent of them died. Nordmann [006] gained the impression that a surgical procedure accelerated the development of necrotizing pancreatitis; this too was perhaps a consequence of the lack of intensive therapy. Parenchymal necrosis varied from 0 to 100 percent of the resected specimen, although at operation all the glands were considered totally or subtotally necrotic. In other words, a large number of surgeons found it hard to distinguish pancreatic and extrapancreatic necroses intraoperatively. The unsatisfactory results of operative treatment led to a move away from surgery at any price towards active conservative therapy [012]. This achieved the first decisive reductions in mortality. The lowering of the overall mortality of necrotizing pancreatitis from around 50 percent to about 25 percent was a great leap forward [014, 015].

In the 1960s and 1970s, the pendulum swung towards rapid operative intervention after diagnosis, but with distinct differences from country to country. In the UK, Watts [016] was

the first to successfully perform resection of the head of the pancreas in hemorrhagic necrotizing pancreatitis. Early resection, right up to total pancreatectomy, was also recommended in France [017-020]. In Germany, the Mainz group first advised early operation, i.e. necrosectomy soon after admission [021], and later recommended delayed surgery in order to be able to at least approximately demarcate the necroses [022]. In the middle of the 1980s, Germany and many other countries followed the indications for surgical management and surgical goals formulated by Beger and his group [023]. The principles of intensive care medicine began to become established. With regard to the pancreas, generous administration of fluids, particularly of human albumin, was a breakthrough [024, 025].

Peritoneal lavage

Corresponding with general clinical experience, it was observed that patients with acute pancreatitis and severe abdominal pain became pain-free immediately after the beginning of peritoneal lavage. This gave rise to the idea that toxic substances could be removed by means of lavage, and thus that lavage could represent a treatment not only for renal insufficiency (a complication of acute pancreatitis), but also for pancreatitis itself. Following the development of a dialysis procedure applicable to rats [026], continuous peritoneal dialysis performed as a treatment for acute experimental taurocholate pancreatitis in the rat significantly prolonged the mean duration of survival and reduced the mortality rate of this experimental disease [027]. Pancreatic ascites fluid given intravenously led to a sharp decrease in blood pressure in healthy dogs [028, 029]. The reason for this effect was unknown, but it was proposed to be partly due to histamine [030, 031]. In a similar experiment, ascites fluid given intraperitoneally also led to a decrease in blood pressure [032]. No follow-up studies were conducted to identify which toxic substance(s) actually led to the fall in blood pressure.

Eight randomized prospective clinical trials evaluating the influence of continuous peritoneal lavage in patients with acute pancreatitis were performed, but led to divergent results [033-040]. A meta-analysis, however, showed that this therapeutic procedure was not associated with any improvement in mortality or morbidity [041]. Furthermore, attempts were made to enhance the efficacy of peritoneal lavage by adding protease inhibitors to the lavage solution. However, neither of two clinical randomized trials showed any significant differences in mortality and morbidity [042, 043].

Principle of inhibition of secretion

Putting the pancreas at rest in acute pancreatitis became a cardinal principle in the 1960s and 1970s. The goal was either to inhibit gastric secretion, thereby indirectly influencing pancreatic secretion, or to inhibit pancreatic secretion directly.

Following reports of possible triggering of acute pancreatitis by cimetidine in the 1970s [044], animal experiments were carried out to ascertain whether this H₂ receptor antagonist could be harmful. Hadas et al [045] found that cimetidine increased the mortality of sodium taurocholate pancreatitis in rats tenfold. However, these findings could not be duplicated in other animal studies [046, 047]. A meta-analysis carried out several years ago [048] covered five randomized controlled trials written in English comparing the effects of H₂ receptor antagonists with those of placebo [049-053]. This meta-analysis [047] showed that cimetidine was not more effective than placebo in reducing acute pancreatitis-related complications and the duration of pain; rather, the use of cimetidine for acute pancreatitis could be associated with higher rates of complications and pain. Thereafter, inhibition of acid secretion was indicated only in severe acute pancreatitis to prevent bleeding from ulcers.

Atropine inhibits gastric and pancreatic secretions and exerts a spasmolytic action on the sphincter of Oddi. These properties would seem to make administration of atropine an ideal therapeutic intervention in acute pancreatitis. These effects cannot be achieved, however, with the dosage that can be administered, i.e. 4×0.5 mg/24 h. Higher dosages lead to adverse effects such as amplified symptoms of ileus, tachycardias and atropine psychoses; therefore, particularly after the sole controlled study [054] showed no favorable effect of atropine on the course of acute pancreatitis, this substance was no longer employed. Interestingly, very early reports of the complications of acute pancreatitis included pancreatic encephalopathy, but later, when atropine was no longer used, this adverse effect was not mentioned. Perhaps there is no pancreatic encephalopathy, and the complication that was observed was in fact an atropine psychosis.

Glucagon inhibits the ecbolic and to a lesser extent the hydrokinetic pancreatic secretion. After a first report on the action of glucagon in patients with acute pancreatitis seemed to show a beneficial effect [055], numerous other investigations were conducted. One study showed a favorable influence of glucagon on pancreatitis in pig, but this could not be confirmed in other animal models and species [056-060]. Later clinical controlled studies showed no beneficial effect on the course or the mortality of human acute pancreatitis [061-068]. Therefore, the administration of glucagon in acute pancreatitis was abandoned.

Calcitonin, like glucagon, principally inhibits pancreatic enzyme secretion [069]. However, several clinical studies showed no beneficial effect of calcitonin on the course of acute pancreatitis [070-072].

Principle of inhibition of autodigestion

After numerous studies had failed to show any significant decrease in the mortality of patients with acute pancreatitis under treatment with aprotinin [073], one team of investigators [074] was able to reduce the mortality rate considerably by administering a high dose of aprotinin in biliary and idiopathic acute pancreatitis. However, these findings were not confirmed in subsequent trials [075].

The failure of aprotinin, the first antiprotease drug to be used in clinical trials, was attributed to the molecular weight of the substance (6,500 Da), which was considered too high to permit uptake in pancreatic acinar cells and thus inhibition of intracellular proteases. A low-molecular-weight antiprotease, gabexate-mesilate (417 Da), was synthesized and showed promise. However, controlled studies found that this substance was not effective in preventing complications and mortality in acute pancreatitis [076-078]. A meta-analysis on the effectiveness of gabexate-mesilate in acute pancreatitis confirmed that it did not affect mortality or the incidence of complications, including those that required surgery, and thus cannot be recommended [079].

Antifibrinolytics such as epsilon-aminocaproic acid and its derivatives, transexamic acid, and p-aminomethylbenzoic acid inhibit plasmin and trypsin and also increase the antitrypsin activity of plasma. In a single controlled study, epsilon-aminocaproic acid had no effect on the course of the disease [080].

Treatment of acute pancreatitis with fresh-frozen plasma, given to replenish important circulating proteins, particularly the naturally occurring antiprotease system, seemed to be successful in an uncontrolled study [081]. However, multiple clinical trials of low- and high-volume fresh-frozen plasma therapy showed no differences between treated and nontreated patients [082, 083].

Principle of inhibition of inflammation

Indomethacin inhibits prostaglandin production in vivo and is a very powerful inhibitor of phospholipase A₂ activity in serum in patients with acute pancreatitis [084]. In the 1970s, oral or intramuscular administration of indomethacin before or shortly after the triggering of an acute pancreatitis attack in rats markedly reduced mortality [085]. Several years later, in a controlled double-blind study, a Danish group achieved a clear reduction in the frequency and intensity of pain in patients with acute pancreatitis by administering indomethacin suppositories 50 mg twice daily for 7 days [086].

Summary of a century of management of acute pancreatitis

The greatest change in the treatment of acute pancreatitis is that surgery has been transformed from an immediate measure in necrotizing disease to a late intervention. Although large prospective, multicenter studies are still lacking, the pendulum has swung towards conservative treatment: across the world, conservative measures are tried first even in the presence of infected necroses. Surgical intervention is reserved for complications in the later stages of the disease. Peritoneal lavage has been discontinued owing to its lack of clinical efficacy. It is unfortunate that no investigations were carried out to establish which substances are responsible for the hypotensive action of ascites fluid; a new principle of therapy might have emerged. The principle of inhibition of autodigestion has been completely abandoned, at least in most countries. Endoscopic sphincterotomy has an established role, while cholecystectomy to prevent recurrence of biliary pancreatitis is undisputed but is still performed too infrequently [087].

Some pancreatological stars of the 20th century

Joan Braganza

Dr. Joan Braganza, a world expert in the field of chronic pancreatitis, proposed a new template for its pathogenesis based on the role of free radical pathology, in particular the heightened but unmitigated oxidative detoxification reactions via cytochromes P450. Dr. Braganza has gone on to show how pancreatic damage in cystic fibrosis, acute pancreatitis and pancreatic cancer fit into the scheme, paving the way for new treatment modalities. She graduated in Bombay in 1966, having never seen a patient with chronic pancreatitis, but in January 1968 she found herself in a chronic pancreatitis referral unit at the Manchester Royal Infirmary. Its chief was Henry Howat who had introduced pancreozymin – discovered by Alan Harper and colleagues at the University – as an adjunct in the classical secretin test. The finding of secretory impairment was the only way to diagnose chronic pancreatitis pre-operatively. It was clear that chronic pancreatitis was equated with alcoholism, and that duct decompression or resective surgery was the mainstay of treatment for agonizing pain, in apparent support of the notion that calcifying protein plugs in the duct system were the seminal problem that led to strictures, compromising acinar function. In May 1969, soon after she had obtained the MRCP, domestic tragedy forced her to resign. Howat had an ongoing research programme on gastric and pancreatic secretion in the anaesthetised cat in response to caerulein analogues. She synthesised the research data into an MSc thesis and wrote four papers for *The Journal of Physiology*. Her new finding was that Boots secretin – but not the purer gastro-intestinal-hormone product from Stockholm – had a potent pepsin-stimulating effect which was not due to a non-specific increase in blood flow, as shown by cannulating the hepatic artery. Howat retired in 1976. Now, with responsibility for some 100 patients with chronic pancreatitis, she switched focus to its etiology. The threefold increase in annual admissions since 1955 was impressive, as was the younger age at presentation. Alcohol was not implicated in 50 percent of the cases. Instead, a threefold increase in the UK

consumption of corn oil, essentially linoleic acid, had been documented. In chronic pancreatitis patients, there was a striking excess of copper and also bilirubin soon after secretin, and higher serum levels, too, of caeruloplasmin [Clini Sci 1981, Clin Chem Acta 1981]. The idea that these changes reflected a compensation for excessive copper absorption, in line with a failing pancreas, was supported by rat experiments. The quest for an explanation led to London's Thomas Dormandy – a pioneer in the field of free radical pathology. In patients with chronic pancreatitis it was found high concentrations in secretin-stimulated bile or duodenal aspirate of several lipidbased products of free radical oxidation [Lancet 1983]. Now, the copper aberrations could be interpreted as indicating the mobilisation of hepatic antioxidant defence. Moreover, secretin was known to increase the activity of microsomal cytochromes P450 (CYP) and bilirubin transferases in rat liver. Not only are CYP induced by alcohol and corn oil-rich diets, but they detoxify numerous xenobiotics, in the process generating reactive oxygen species and sometimes, as in paracetamol poisoning, also reactive xenobiotic species. Thus, it was proposed that pancreatic disease – not only chronic pancreatitis but also acute pancreatitis and cancer – may be a casualty of hepatic “detoxification”, when reactive material enters the gland in refluxed bile or duodenal juice [Lancet 1983]. David Dreiling was the first to see the potential merit of this hypothesis. Pharmacokinetic studies confirmed an induction of CYP – especially the CYP1 family – in the majority of patients, including those with idiopathic disease. This was rationalized by cigarette smoke constituents, but especially, by regular close exposure to occupational volatile hydrocarbons [Int J Pancreatology 1986, Occup Environ Med 1994]. These would strike the pancreas directly, bypassing the protective liver sieve. Thus, CP – and also drug-related acute pancreatitis and pancreatic cancer – might actually reflect direct oxidant damage via reactivated pancreatic CYP. That could be the reason why surgical diversion of toxic bile failed to abort attacks. Studies of habitual diets in patients with idiopathic chronic pancreatitis, by reference to a CYP1-induced control group on anticonvulsants, underlined their lower intakes of selenium, vitamin C and methionine. These micronutrients interact in the methionine transsulphuration pathway that yields glutathione and other detoxifiers. Several enzymes in this pathway are vulnerable to oxidative stress, as are the components of the signal transduction route towards exocytosis in the pancreatic acinar cell. 1990 saw the publication of dr Braganza's 20- week placebo-controlled switch-over trial of antioxidant therapy in chronic pancreatitis [Aliment Pharmacol Therap 1990]. Pain reduction was accompanied by a fall in serum 9,11,LA' and correction of the poor antioxidant status. These and other concepts were reviewed at a symposium that organized at the 1998 World Gastroenterology Congress in Vienna by dr Braganza [Digestion 1998; 59(suppl 4)]. Another high point was the finding – in collaboration with Maurice Super and Martin Schwartz – of an increased frequency of mutations in the cystic fibrosis transmembrane regulator (CFTR) gene in patients with chronic pancreatitis [N Eng J Med 1998]. She record the invaluable input during her 25-year “radical journey” of numerous scientists – in physiology (Maynard Case, Sigrid RuMeettishauser), transplant immunology (Ian Hutchinson), surgical science (Anders Borgström), bacteriology (Louis Quesnel), pharmacy (Brian Houston, Martin Jones, John Fell, Frank Leach), biochemistry (Frank Steven, Jop Ubbink, Jessica Douglas, Lance Sandle, Iain Laing), pharmacogenetics (Jeffrey Idle), medical physics (Harbans Sharma), pathology (John Foster, Najeeb Haboubi, Iona Jeffrey), medical statistics (Linda Hunt, Roseanne McNamee, Chris Main), occupational health (Tim Lee, Ian Leck, Nicola Cherry), chemistry (Giocomo Sturniolo, George Smith, Philip Day), dietetics (Patricia Rose, Helen Worthington) and free radical pathology (Thomas Dormandy, John Gutteridge, John Butler) [088].

John A Williams

Dr John A Williams is one of the world's leading physiologists working on signal transduction mechanisms in pancreatic acinar cells. He is worldwide recognized for his contribution to many areas of pancreatology, especially the understanding of GI hormone regulation of pancreatic exocrine function. Having grown up in a small college town in Washington state

with an interest in science and natural history he aimed towards a career in medicine, in part because he received a lot of social reinforcement when he mentioned it. He took the chance to enter a summer research program prior to starting medical school at the University of Washington. By a somewhat convoluted logic he was placed in an electrophysiology laboratory and proceeded to fall in love with laboratory research. then took a year off to do research in the middle of medical school after which his mentor, J Walter Woodbury asked him if he wanted to take another year off and earn a PhD. His thesis was on the electrophysiology of the thyroid. He did a 2-year stint in the U.S. Public Health Service at NIH to fulfill my military obligation where he carried out research on thyroid secretion with Jan Woolf. They then moved to Cambridge in the UK where he worked in the laboratory of Keith Mathews adjacent to another postdoc, Ole Petersen, who had come from Copenhagen and was recording intracellularly from pancreas. It then became apparent to that the exocrine pancreas was an ideal tissue with which to study regulated secretion in that it was homogeneous with one predominant cell type and that there were simple assays to measure the enzymatic activity of the secretory products. Petersen and Williams carried out a still (2010) cited study showing the release of intracellular calcium and its relationship to secretion in perfused pancreatic segments stimulated with CCK-PZ. After an enjoyable stay in Cambridge, Williams moved to San Francisco where a faculty position was waiting. Over the first 5 years there, his research work shifted almost entirely to the pancreas. He was able to bridge his interests by studying the effects of insulin on acinar cells and the action of gastrointestinal hormones especially CCK on the exocrine pancreas [089].

ANATOMY, DEVELOPMENT, EMBRYOLOGY AND ANOMALIES

Development

Studies in both humans and rodents have found that insulin(+) cells appear within or near ducts of the adult pancreas, particularly following damage or disease, suggesting that these insulin(+) cells arise de novo from ductal epithelium. It has been found that insulin(+) cells are continuous with duct cells in the epithelium that makes up the hyperplastic ducts of both chronic pancreatitis and pancreatic cancer in humans. Therefore, it was tested the hypothesis that both hyperplastic ductal cells and their associated insulin(+) cells arise from the same cell of origin. Using a mouse model that develops insulin(+) cell-containing hyperplastic ducts in response to the growth factor TGFalpha, it was performed genetic lineage tracing experiments to determine which cells gave rise to both hyperplastic ductal cells and duct-associated insulin(+) cells. It was found that hyperplastic ductal cells arose largely from acinar cells that changed their cell fate, or transdifferentiated, into ductal cells. However, insulin(+) cells adjacent to acinar-derived ductal cells arose from pre-existing insulin(+) cells, suggesting that islet endocrine cells can intercalate into hyperplastic ducts as they develop. It was concluded that apparent pancreatic plasticity can result both from the ability of acinar cells to change fate and of endocrine cells to reorganize in association with duct structures [090].

Centroacinar cells

The question of whether dedicated progenitor cells exist in adult vertebrate pancreas remains controversial. Centroacinar cells and terminal duct (CA/TD) cells lie at the junction between peripheral acinar cells and the adjacent ductal epithelium, and are frequently included among cell types proposed as candidate pancreatic progenitors. However these cells have not previously been isolated in a manner that allows formal assessment of their progenitor capacities. It has now been found that a subset of adult CA/TD cells are characterized by high levels of ALDH1 enzymatic activity, related to high-level expression of both Aldh1a1 and Aldh1a7. This allows their isolation by FACS using a fluorogenic ALDH1 substrate. FACS-isolated CA/TD cells are relatively depleted of transcripts associated with differentiated pancreatic cell types. In contrast, they are markedly enriched for transcripts encoding Sca1, Sdf1, c-Met, Nestin, and Sox9, markers previously associated with progenitor populations in embryonic pancreas and other tissues. FACS-sorted CA/TD cells are uniquely able to form self-renewing "pancreatospheres" in suspension culture, even when plated at clonal density. These spheres display a capacity for spontaneous endocrine and exocrine differentiation, as well as glucose-responsive insulin secretion. In addition, when injected into cultured embryonic dorsal pancreatic buds, these adult cells display a unique capacity to contribute to both the embryonic endocrine and exocrine lineages. Finally, these cells demonstrate dramatic expansion in the setting of chronic epithelial injury. These findings suggest that CA/TD cells are indeed capable of progenitor function and may contribute to the maintenance of tissue homeostasis in adult mouse pancreas [091].

Acinar, ductal and endocrine interaction

Studies in both humans and rodents have found that insulin(+) cells appear within or near ducts of the adult pancreas, particularly following damage or disease, suggesting that these insulin(+) cells arise de novo from ductal epithelium. It was found that insulin(+) cells are continuous with duct cells in the epithelium that makes up the hyperplastic ducts of both chronic pancreatitis and pancreatic cancer in humans. Therefore, it was tested the

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Pacinian corpuscles

To analyze the immunohistochemical profile of the human pancreatic pacinian corpuscles in comparison with that of the cutaneous pacinian corpuscles and to study a pacinilike corpuscle found in the adventitia of a pancreatic artery it was used immunohistochemistry to detect specific antigens for corpuscular constituents, specific antibodies for the identification of A δ - and C-sensory fibers and for the detection of several growth factor receptors, and some members of the degenerin/epithelial Na channel superfamily of proteins. Approximately 62 percent of pancreatic pacinian corpuscles have 2 to 10 axonic profiles each enclosed by its own inner core: 1 or 2 of these axonic profiles displayed RT-97 immunoreactivity (specific marker of mechanical axons). The cutaneous pacinian corpuscles showed not more than 2 axonic profiles with identical immunohistochemical characteristics. The expression of glial fibrillary acidic protein, epithelial membrane antigen, and tyrosine receptor kinase B was different between pancreatic and cutaneous pacinian corpuscles; the pattern of distribution of degenerin/epithelial Na channel proteins was identical in both cases. The arterial pacinilike corpuscles displayed a specific immunohistochemical profile. It was concluded that pancreatic pacinian corpuscles slightly differ from the cutaneous ones, and these differences could be related to topography, growth factor requirements, or function of pacinian corpuscles in the pancreas [093].

Pancreatic isthmus

Pancreatic isthmus method anastomosis following pancreatic resection is an important factor of postoperative fistula formation. While the anatomy and vascular supply of the pancreatic head have been studied in detail, little is known about the morphology of the pancreatic isthmus. The authors determine the anatomy and morphology of the pancreatic isthmus. Ninety-nine consecutive cadaveric pancreatic specimens were taken during standard autopsy. Organs were transected at the isthmus and pancreatograms and microscopic specimens of the transection plane were analyzed. The mean size of the Wirsung duct at the isthmus was 2.9 mm (\pm 0.87 mm, from 1.4 to 6 mm). The main pancreatic duct was located approximately in the middle of the pancreatic cross-section plane in almost all specimens. The total number of second-degree pancreatic ducts visible on pancreatograms within the isthmus was 1.8 (\pm 1.00, from 0 to 4) and 1.8 (\pm 1.4, from 0 to 5) on microscopic analysis. It was concluded that the presence of second-degree pancreatic ducts at the transection site might favor the use of a pancreatocentric anastomosis with stump invagination to reduce the risk of anastomotic leakage [094].

Retroperitoneum

The extraperitoneal space extends between peritoneum and investing fascia of muscles of anterior, lateral and posterior abdominal and pelvic walls, and circumferentially surrounds the abdominal cavity. The retroperitoneum, which is confined to the posterior and lateral abdominal and pelvic wall, may be divided into three surgicoanatomic zones: centromedial, lateral (right and left), and pelvic. The preperitoneal space is confined to the anterior abdominal wall and the subperitoneal extraperitoneal space to the pelvis. In the extraperitoneal tissue, condensation fascias delineate peri- and parasplanchnic spaces. The former are between organs and condensation fasciae, the latter between this fascia and investing fascia of neighboring muscles of the wall. Thus, perirenal space is encircled by renal fascia, and pararenal is exterior to renal fascia. Similarly for the urinary bladder, paravesical space is between the umbilical prevesical fascia and fascia of the pelvic wall muscles-the prevesical space is its anterior part, between transversalis and umbilical prevesical fascia. For the rectum, the "mesorectum" describes the extraperitoneal tissue bound by the mesorectal condensation fascia, and the pararectal space is between the latter and the muscles of the pelvic wall. Perisplanchnic spaces are closed, except for neurovascular pedicles. Prevesical and pararectal (presacral) and posterior pararenal spaces are in the same anatomical level and communicate. Anterior to the anterior layer of the renal fascia, the anterior interfascial plane (superimposed and fused mesenteries of pancreas, duodenum, and colon) permits communication across the midline. Thus parasplanchnic extraperitoneal spaces of abdomen and pelvis communicate with each other and across the midline [095].

Wirsung duct duplication

The human exocrine pancreas develops embryologically from the ventral and the dorsal anlagen that evaginate from the primitive foregut during the fifth week of gestation. The dorsal anlage will form the superior part of the head, the body, and the tail of the pancreas, whereas the ventral anlage becomes the inferior part of the head and the uncinata process. Each bud has its own duct; as the buds fuse, their ducts anastomose. Duplication anomalies of the main pancreatic duct are uncommon, reportedly 5-6 percent, whereas those involving the parenchyma from the dorsal and the ventral anlagen are extremely rare. A case described complete duplication anomaly of the Wirsung duct in an asymptomatic patient. It was proposed the term *ansa pancreatica*, which is characterized by obliteration of the accessory pancreatic duct at the point of connection with the ventral pancreatic duct and replacement of it by an additional arched communication between the dorsal and the ventral duct systems. *Ansa pancreatica* is formed postembryologically to compensate for the absence of the duct of Santorini. The patency of the *ansa pancreatica* was reported to be 20-33 percent. The authors suggested that a patent accessory pancreatic duct may lower the pressure in the main pancreatic duct by draining through the minor papilla and might therefore prevent the attacks of acute pancreatitis. This hypothesis could explain why in our case, despite the complex anatomical variation, the patient did not develop any episode of acute pancreatitis and there was no evidence of chronic pancreatitis [096].

Vessel anatomy

Development of the pancreatic arcades

From human fetuses between 8-30 weeks, it was described the topographical anatomy of the vessels, bile duct, duodenum as well as the ventral and dorsal primordia of the pancreatic head with an aid of pancreatic polypeptide immunohisto-chemistry. The contents of the

hepatoduodenal ligament crossed the superior side of the pylorus. Moreover, the right hepatic artery originating from the superior mesenteric artery ran along the superior aspect of the pancreatic head. An arterial arcade, corresponding to the posterior pancreaticoduodenal arteries, encircled the superior part of the pancreatic head, whereas another arcade, corresponding to the anterior pancreaticoduodenal arteries, surrounded the inferior part. The dorsal promordium of the pancreas surrounded and/or mixed the ventral primordium at 13-16 weeks. Thus, both arterial arcades were likely to attach to the dorsal primordium. It was concluded that the fetal anatomy of the pancreaticoduodenal vascular arcades as well as that of the hepatoduodenal ligament were quite different from adults in topographical relations. Thus, in the stage later than 30 weeks, further rotation of the duodenum along a horizontal axis seemed to be required to move the pylorus posterosuperiorly and to reflect the superior surface of the pancreatic head posteriorly. However, to change the topographical anatomy of the superior and inferior arterial arcades into the final position, re-arrangement of the pancreatic parenchyma might be necessary in the head [097].

Pancreatic arteries

The pancreas has complex arterial supplies. Therefore, special attention should be paid in pancreatic arterial intervention for patients with acute pancreatitis and pancreatic carcinomas. Knowledge of pancreatic arterial anatomy and arterial territory is important not only to perform pancreatic arterial intervention, but to read the pancreatic angiography and cross-sectional image. It was reviewed 226 selective abdominal angiography and CT scans during selective arteriography (CTA) of common hepatic artery, superior mesenteric artery, splenic artery, or peripancreatic arteries including posterior superior pancreaticoduodenal artery, anterior superior pancreaticoduodenal artery, inferior pancreaticoduodenal artery, and dorsal pancreatic artery. CTA images were evaluated to clarify the cross-sectional anatomy of the pancreatic arterial territory. Variations of the peripancreatic arteries were also investigated [098].

Pancreaticoduodenectomy entails ligation of vascular arcades arising from the celiac and superior mesenteric arteries. These are known to have anatomical variations. One study was aimed at analyzing the spectrum of arterial anomalies and their clinical impact on the procedure itself. The study included 200 consecutive patients who underwent a pancreaticoduodenectomy between 2003 and 2009 after excluding those having distant metastases or local unresectability. Fifty-three patients (26.7 %) had arterial anomalies. The complexity of the surgery was determined by the course of these arteries. The mean duration of surgery was 420 ± 32 minutes in patients with arterial anomalies versus 370 ± 39 minutes in those with a normal arterial anatomy. Fifty-one out of 53 (96 %) patients underwent pancreaticoduodenectomy with negative resection margins. The pancreaticoduodenectomy was abandoned in two cases due to patient- and tumor-related factors. This means that during pancreaticoduodenectomy, arterial anomalies can increase operative complexity but do not usually compromise the safety of the procedure or its oncological outcome [099].

Pancreatic veins

To date the anatomy of the intrapancreatic and peripancreatic veins using multidetector-row CT (MDCT) was not assessed. The object of this study is to establish 3D CT anatomy of these veins. A total of 100 consecutive patients who underwent abdominal triple-phase CT using 16-detector MDCT were retrospectively reviewed. The anatomical variations of the peripancreatic and intrapancreatic veins were assessed. Among the 100 cases, 42 cases (42 %) had a single posterior superior pancreaticoduodenal vein crossing the ventral side of the common bile duct, while 30 cases (30 %) had an uncinata vein running upward behind the medial side of the pancreatic. In the pancreatic head and body/tail area, there were many small veins that directly entered the superior mesenteric or splenic vein. In 59 cases (59 %),

the centro-inferior pancreatic vein ran transversely along the inferior surface of the pancreatic body and drained the anterior or inferior parts of the pancreatic body, mainly into the splenic vein. Many variations exist in the running patterns of intrapancreatic veins as well as peripancreatic veins. Recognition of abnormalities of intrapancreatic veins on CT in the light of normal CT anatomy may contribute to the interpretation of pathological conditions of the pancreas [100].

Superior mesenteric vein

It is important to be aware of mesenteric venous variants to perform peripancreatic surgery. It was now investigated the usefulness of 3-dimensional (3-D) portography. Vessels were reconstructed using computer software in 102 patients undergoing multidetector-row computed tomography (MDCT) scheduled for gastrointestinal or hepatobiliary-pancreatic surgery. The superior mesenteric vein (SMV) was composed of single and double trunks around the splenoportal confluence in 78 and 24 patients, respectively. The inferior mesenteric vein joined the splenic vein (69 %), SMV (19 %), and splenoportal confluence (8 %). The left gastric vein joined the splenic vein (46 %), portal vein (39 %), and splenoportal confluence (15 %). Seventy-nine patients showed a gastrocolic trunk, mostly composed of the right gastroepiploic vein and veins from the colonic hepatic flexure. Intraoperative findings were identical to 3-D diagnosis in 68 gastrectomized and 9 pancreatectomized patients. The authors concluded that although mesenteric venous tributaries are complex, 3-D portography is helpful for surgeons to safely perform peripancreatic surgery [101].

Celiac axis and common hepatic artery variations

To identify and evaluate the spectrum and prevalence of celiac axis (CA) and common hepatic artery (CHA) variations by using spiral computed tomography (CT) and digital subtraction angiography (DSA). It was an institutional review board approval that was obtained, and the requirement for informed patient consent was waived. The findings in 5002 patients who underwent spiral CT and DSA were retrospectively evaluated. CHA was defined as an arterial trunk containing at least one segmental hepatic artery and the gastroduodenal artery. The pattern of the aortic origin of the branches of the CA and superior mesenteric arteries was analyzed. The CHA anatomy was then investigated. Of 15 possible types of CA variation, 13 types were identified. A normal CA was noted in 4457 (89 %) of the 5002 patients. Twelve types of CA variation were identified in 482 (10 %) patients. In the remaining 63 (1 %) patients, the CA anatomy was classified as ambiguous because the CHA was absent owing to separate origins of the hepatic arteries and the gastroduodenal artery (n=55) or because the origin of the CHA could not be determined owing to persistent anastomotic channels (n=8). Seven CHAs originating from the normal CA had a retroportal (n=6) or transpancreatic (n=1) course. All eight CHAs originating from the left gastric artery passed the fissure of the ligamentum venosum. The 148 CHAs originating from the superior mesenteric artery showed diverse relationships with the pancreas – being supra-, trans-, or infrapancreatic – and the superior mesenteric-portal venous axis – being pre- or retroportal. The 20 CHAs originating from the aorta had a normal suprapancreatic preportal course [102].

Prepancreatic portal vein

Prepancreatic portal vein is an extremely rare congenital anomaly. It is even rarer in the setting of intestinal nonrotation. It was reported a case of prepancreatic portal vein in a 71-year-old female with nonrotation who presented with a pancreatic adenocarcinoma in the tail of the pancreas who underwent a distal pancreatectomy and splenectomy. This anomaly was identified prior to surgery on CT scan of the abdomen [103].

Portal annular pancreas is a rare congenital anomaly resulting from fusion of the pancreatic parenchyma around the portal vein/superior mesenteric vein. It is asymptomatic, but could

have serious consequences during pancreatic surgery, if unrecognized. It was reported a 51-year-old male who underwent a pancreaticoduodenectomy for periampullary carcinoma. After division of the pancreatic neck, a sheath of tissue was found posterior and extending to the left of the portal vein. When this tissue was divided, a large duct was encountered; this duct communicated with the main pancreatic duct. On review of the CT images, the main pancreatic duct was seen to be passing posterior to the portal vein and a smaller accessory pancreatic duct was present anterior to the portal vein. This variant of portal annular pancreas has not yet been reported during pancreaticoduodenectomy and we propose a new classification for this fusion anomaly [104].

Heterotopic pancreas

The case of a 75-year-old female suffering from recurrent abdominal pain and nausea is presented. Ultrasound showed gallstones without inflammation of the gallbladder. The patient underwent laparoscopic cholecystectomy and her symptoms resolved. Histological examination of the operation specimen disclosed heterotopic pancreatic tissue within the cystic duct. An accurate clinical diagnosis of pancreatic heterotopia is difficult. The deep submucosal or intramural location of the lesion may hamper retrieval of representative biopsy material. Indications for surgery or endoscopic resection include symptomatic lesions as well as cases of unclear histological examination in order to distinguish pancreatic heterotopia from other tumors [105].

Ectopic pancreas in the thoracic cavity is uncommon. It was reported two patients who had large cystic or cystic-solid masses containing pancreatic tissue in the thorax. Their clinical presentation, imaging, and pathologic findings were described. Both patients underwent total surgical resection of the masses, with no recurrence [106].

A 26-year-old woman presented with symptoms of bowel obstruction. An emergent computed tomography (CT) scan was performed which showed ileoileal intussusceptions due to a fatty nodule. Exploratory laparotomy and removal of the involved small bowel was performed. The pathology showed the leading point of the intussusception to be ectopic pancreas with abundant fatty infiltration [107].

Gastric duplication cysts are often associated with microscopic evidence of ectopic pancreatic tissue on their submucosal surface and, less commonly, on the subserosal surface. It was presented an unusual case of a gastric duplication cyst with finger-like projections and a large heterotopic pancreas on the serosal surface of the cyst in a 30-year-old female [108].

Heterotopic pancreas (HP) in stomach is a rare pathological entity that poses clinical dilemma for diagnosis and management. It carries a risk of developing serious benign and malignant complications. It was presented a case of 37-year-old lady who presented with dyspeptic symptoms and was found to have a 1.5 cm umblicated lesion in the distal stomach on gastroscopy. Endoscopic biopsy showed normal gastric mucosa and CT scan of stomach did not show any specific abnormality. A laparoscopic wedge excision was performed. Histology showed features of heterotopic pancreas [109].

Pancreatic heterotopia has been described at several abdominal and intrathoracic locations, most commonly in the stomach and upper part of the small intestine. Its occurrence in the rectum is unusual, and malignant transformation in the rectum has not been reported. It was reported a case of ductal adenocarcinoma arising in a rectal pancreatic heterotopia in a 42-year-old woman with delayed local recurrence. The tumor was composed of well to moderately differentiated ductal adenocarcinoma infiltrating through the full thickness of the anorectal wall with extension into the vaginal septum. A focus of ectopic pancreas consisting

of exocrine acini and small ducts adjacent to the tumor with some ducts showing mild to severe dysplasia reminiscent of pancreatic intraepithelial neoplasia was also observed. Although our literature search found 31 documented reports of tumors arising in the heterotopic pancreas, the present case is the first case of ductal adenocarcinoma arising in a focus of pancreatic heterotopia in the rectum [110].

PHYSIOLOGY

Interstitial cells of Cajal

Ramon y Cajal discovered interstitial cells in the pancreas associated with intrinsic nerves. It was now the aim to provide evidence for or against the hypothesis that the pancreatic duct harbors interstitial cells of Cajal that may function as pacemakers for duct motility. It was used immunohistochemistry using c-Kit as the interstitial cells of Cajal marker and protein gene product 9.5 for nerves. Electron microscopy further characterized the cells and their interrelationships. c-KitYpositive cells were associated with smooth muscle cells and nerve fibers of the duct wall and were rich in mitochondria, rough endoplasmic reticulum, and intermediate filaments; they possessed occasional caveolae and had a discontinuous basal lamina. They were connected by small gap junctions to each other and to smooth muscle cells. c-KitYpositive cells around large blood vessels were similar. c-KitYpositive cells within acini were similar in structure but were not associated with smooth muscle cells. It was concluded that the c-KitYpositive cells around the main duct were identified as interstitial cells of Cajal and have the morphological criteria to likely function as pacemaker cells for the previously observed spontaneous rhythmic pancreatic duct contractions. Interstitial cells of Cajal around the large blood vessels likely affect vessel wall rhythmicity [111].

Bicarbonate

Pancreatic bicarbonate (HCO_3^-) secretion is important for a healthy pancreas as well as digestive physiology. However, how human pancreatic duct cells secrete copious amounts of HCO_3^- has long been a puzzle. It was now reported that a dynamic increase in the cystic fibrosis transmembrane conductance regulator (CFTR) HCO_3^- permeability by intracellular Cl^- concentration ($[\text{Cl}]_i$)-sensitive mechanisms plays a pivotal role in pancreatic HCO_3^- secretion. The role of $[\text{Cl}]_i$ -sensitive kinases in CFTR-mediated HCO_3^- transport was examined in heterologous expression systems, PANC1 human pancreatic duct cells, and human and guinea pig pancreatic tissues using an integrated molecular and physiologic approach. In human pancreatic tissues, CFTR-positive duct cells abundantly expressed with-no-lysine (WNK1) kinase, oxidative stress-responsive kinase 1 (OSR1), and sterile 20/SPS1-related proline/alanine-rich kinase (SPAK), which are known to be activated by low $[\text{Cl}]_i$. Interestingly, CFTR activation rapidly decreased $[\text{Cl}]_i$ in response to luminal Cl^- depletion in polarized PANC1 human pancreatic duct cells. Notably, the WNK1-mediated OSR1 and SPAK activation by low intracellular chloride concentration strongly increased CFTR HCO_3^- permeability in CFTR-transfected HEK 293T, PANC1, and guinea pig pancreatic duct cells, making CFTR primarily an HCO_3^- channel, which is essential for the secretion of pancreatic juice containing HCO_3^- at a concentration greater than 140 mmol/L. In contrast, OSR1 and SPAK activation inhibited CFTR-dependent $\text{Cl}^-/\text{HCO}_3^-$ exchange activity that may reabsorb HCO_3^- from the high HCO_3^- -containing pancreatic juice. These results indicate that the intracellular concentration of sensitive activation of the WNK1-OSR1/SPAK pathway is the molecular switch to generate HCO_3^- rich fluid in the human pancreatic duct [112].

Insular-acinar axis

Although the role of the islets in the regulation of acinar cell function seemed a mystery to investigators who observed their dispersion among pancreatic acini, over time an appreciation for this intricate and unique structural arrangement has developed. The last three decades have witnessed a steadily growing understanding of the interrelationship of

the endocrine and the exocrine pancreas. The islet innervation and vascular anatomy have been more fully characterized and provide an appropriate background for our current understanding. The interrelationship between the endocrine and exocrine pancreas is mediated by islet-derived hormones such as insulin and somatostatin, other humoral factors including pancreastatin and ghrelin, and also neurotransmitters (nitric oxide, peptide YY, substance P, and galanin) released by the nerves innervating the pancreas. Although considerable progress has been achieved, further work is required to fully delineate the complex interplay of the numerous mechanisms involved. The dominant role played by insulin and somatostatin on exocrine secretion sheds light on the influence of the various neuropeptides on amylase secretion [113].

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Trypsinogen

One study led to the development of monoclonal antibodies and time-resolved immunofluorometric methods recognizing human trypsinogen-1 and -2, respectively. Using these methods in normal sera the concentration of trypsinogen-1 was found to be higher than that of trypsinogen-2. However, in acute pancreatitis the concentration of serum trypsinogen-2 was 50-fold higher than in controls, whereas the difference in trypsinogen-1 concentration was only 15-fold. Serum samples from patients who had undergone pancreatoduodenectomy contained trypsinogen-2, while trypsinogen-1 was detected in only one of nine samples. Furthermore, in human ovarian cyst fluids tumor-associated trypsinogen-2 (TAT-2) is the predominant isoenzyme and in mucinous cyst fluids the levels of TAT-2 were associated with malignancy. These results suggest that trypsinogen-2 could be used as a diagnostic marker for acute pancreatitis, its expression is not restricted to the pancreas, and TAT could be involved in ovarian tumor dissemination and breakage of tissue barriers. In ion exchange chromatography, isoelectric variants of the trypsinogen isoenzymes were seen. Mass spectrometric analysis of these revealed that pancreatic trypsinogens are sulfated at tyrosine 154 (Tyr154), whereas TAT-2 from a colon carcinoma cell line is not. Tyr154 is located within the primary substrate binding pocket of trypsin. Thus, Tyr154 sulfation is likely to influence substrate binding. The previously known differences in charge and substrate binding between pancreatic and tumor-associated trypsinogens are suggested to be caused by sulfation of Tyr154 in pancreatic trypsinogens [115].

Desmoplasia

Pancreatic cancer has a very poor prognosis largely due to its early tendency to invade, locally and distantly. Recently, scientists in the field have increasingly focused on the desmoplastic reaction, which is characteristic of most pancreatic cancers. This reaction is associated with proliferation of fibroblastic cells, sometimes outnumbering local tumor cells, and consists of abundant extracellular matrix (ECM) proteins. Importantly, the processes of invasion and metastasis take place within this tumor microenvironment. Stroma and tumor cells exchange signals to modify the local ECM, which subsequently stimulates cell migration and promotes proliferation and survival. Even though recognition of the significance of these microenvironment interactions exists, knowledge on the mechanisms of the interplay among pancreatic cells, myofibroblasts, and the ECM is lacking. Cytokines & Cells Online Pathfinder Encyclopedia (COPE) is a comprehensive website to query information on cytokines, proteins that mediate interactions between cells directly and regulate processes taking place in the extracellular environment, and various cellular pathways. This online encyclopedia is the updated and revised internet version of the printed "Dictionary of Cytokines" from 1995, which is currently out of print. The entries are arranged alphabetically, and they define the function of each known cytokine and cover topics ranging from angiogenesis to apoptosis, survival factors, and chemotaxis [116].

Fatty pancreas

Obesity and insulin resistance cause fatty infiltration of many organs, including the pancreas (pancreatic steatosis, PS) and the liver (nonalcoholic fatty liver disease, NAFLD). In contrast to NAFLD, pathophysiological mechanisms and clinical relevance of PS remain unknown. One study aimed to identify a possible relation between PS and NAFLD. In one study including postmortem collected material of 80 patients, clinical and histological data were collected and revised. Patients with hepatic or pancreatic disease and alcohol abuse were excluded. Nonalcoholic fatty liver disease activity score was used for grading the histology of the liver, whereas pancreatic lipomatosis score assessed PS. Ordinal logistic regression was used to analyze correlations. Interlobular and total pancreatic fat were both significantly related to NAFLD activity score in patients without steatogenic medication. When corrected for body mass index, no relation could be found. Total pancreatic fat was a significant predictor for the presence of NAFLD. Presence of intralobular pancreatic fat was related to nonalcoholic steatohepatitis; however, total fat was not. This study demonstrated that NAFLD and PS are related. This relationship seems to be mediated by general obesity. Intralobular pancreatic fat is associated with nonalcoholic steatohepatitis [117].

Effects of sampling of pancreatic tissues

Little is known about the potential consequences of pancreatic tissue sampling in dogs. The goal of one study was to evaluate changes in serum trypsin-like immunoreactivity and canine-specific pancreatic lipase after pancreatic fine-needle aspiration and surgical biopsy in 27 clinically healthy dogs. Presurgical, ultrasound-guided aspiration of the pancreas was performed with the dogs under sedation. Subsequently, all the dogs underwent intraoperative pancreatic fine-needle aspiration and clamshell biopsy. After euthanasia, pancreata were sectioned for histopathologic evaluation. Serum pancreatic enzyme levels were measured at 3 time points: baseline, after ultrasound-guided aspiration, and after intraoperative aspiration and biopsy. No significant differences were detected among mean serum pancreatic lipase values at any point. Serum trypsin-like immunoreactivity did not change from baseline after ultrasound-guided aspiration but increased significantly after intraoperative sampling. After surgical biopsy, the 20 dogs that had both ultrasound-guided and intraoperative sampling

had a higher mean serum trypsin-like immunoreactivity than the 7 dogs that had only intraoperative samples taken. All 27 pancreata were grossly normal before intraoperative sampling. Pancreatic sampling was associated with increased serum trypsin-like immunoreactivity and mild, peracute necrosis, inflammation, hemorrhage, and fibrin deposition. Tissue damage from sampling was not sufficient to cause an elevation in canine-specific pancreatic lipase in the time frame evaluated [118].

DIABETES OVERVIEW

Type 2 diabetes mellitus (T2DM) affects a large population worldwide. T2DM is a complex heterogeneous group of metabolic disorders including hyperglycemia and impaired insulin action and/or insulin secretion. T2DM causes dysfunctions in multiple organs or tissues. Current theories of T2DM include a defect in insulin-mediated glucose uptake in muscle, a dysfunction of the pancreatic beta-cells, a disruption of secretory function of adipocytes, and an impaired insulin action in liver. The etiology of human T2DM is multifactorial, with genetic background and physical inactivity as two critical components. The pathogenesis of T2DM is not fully understood. Animal models of T2DM have been proved to be useful to study the pathogenesis of, and to find a new therapy for, the disease. Although different animal models share similar characteristics, each mimics a specific aspect of genetic, endocrine, metabolic, and morphologic changes that occur in human T2DM [119].

Incretins

Incretin-based compounds, including glucagon-like peptide-1 receptor agonists and dipeptidyl-peptidase-4 inhibitors, have emerged as a new class of agents for the treatment of type 2 diabetes. In one article, the potential and supporting evidence for extending their use to early type 1 diabetes were reviewed. The rationale relies on the assumption that these drugs, in addition to their action on insulin secretion and glucose regulation, may be effective in preserving and even expanding the beta-cell mass. This assumption is based on data from in vitro and animal studies, with no clear demonstrations in humans. This class of drugs may represent an entirely new approach to the treatment of type 1 diabetes, focused on protection and preservation of beta-cells, an ideal complement to immune interventions inhibiting or modulating the pathogenetic autoimmune process. The ideal candidates for this treatment are patients at the time of clinical onset of type 1 diabetes or individuals with preclinical type 1 diabetes who still have a significant viable beta-cell mass [120].

The incretin hormone, glucagon-like peptide-1 (GLP-1), is now being used in the clinic to enhance insulin secretion and reduce body weight in patients with type 2 diabetes. Although much is already known about the biology of GLP-1, much remains to be understood. Hence, one review considered recent findings related to the potential for enhancing endogenous levels of GLP-1 through selective use of secretagogues and the beneficial cardiovascular, neuroprotective, and immunomodulatory effects of GLP-1, as well as the possible effects of GLP-1 to enhance beta-cell growth and/or to induce pancreatitis or thyroid cancer. Finally, the potential for molecular medicine to enhance the success of GLP-1 therapy in the clinic must be considered. A better understanding of the fundamental biology of GLP-1 may lead to new therapeutic modalities for the clinical use of this intestinal hormone [121].

In diabetes type 2

Progressive deterioration of beta-cell function is a hallmark of type 2 diabetes mellitus (DM). Together with increasing insulin resistance in peripheral tissues (in both the liver and the skeletal muscle), the inability of pancreatic insulin secretion to manage fasting and postprandial glucose levels results in hyperglycemia. Currently available oral antidiabetes agents improve glycemic parameters, but no single drug addresses the numerous pathophysiologic defects known to contribute to hyperglycemia in patients with type 2 DM. Dysregulation in the incretin system is another component of the pathophysiologic processes that lead to DM. Agents used to correct defects in the incretin system, such as glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors, offer the potential to restore

glucose-dependent insulin secretion and improve beta-cell function. Glucagon-like peptide 1 receptor agonists also promote weight loss and provide beneficial effects on cardiovascular risk factors. A new approach that promotes the selection of pharmacotherapy for the treatment of patients with DM, with the goal of slowing or reversing the natural history of the disease, may be in order. Clinicians can select agents to address specific pathophysiologic defects to improve glycemia, with the hope of preventing the development of complications [122].

GENERAL DIAGNOSTICS

Radiation risks

Low-dose ionizing radiation from medical imaging has been indirectly linked with subsequent cancer. Computed tomography (CT) is the gold standard for defining pancreatic necrosis. The primary goal was to identify the frequency and effective radiation dose of CT imaging for patients with necrotizing pancreatitis. All patients with necrotizing pancreatitis (2003-2007) were retrospectively analyzed for CT-related radiation exposure. Necrosis was identified in 18 percent (238/1290) of patients with acute pancreatitis (mean age 53 years; hospital/ICU length of stay 23/7 days; mortality 9 %). A median of five CTs/patient (interquartile range, IQR, 4) were performed during a median 2.6-month interval. The average effective dose was 40 mSv per patient (equivalent to 2,000 chest X-rays; 13.2 years of background radiation; one out of 250 increased risk of fatal cancer). The actual effective dose was 63 mSv considering various scanner technologies. CTs were infrequently (20 %) followed by direct intervention (199 interventional radiology, 118 operative, 12 endoscopic) (median 1; IQR 2). Magnetic resonance imaging did not have a CT-sparing effect. Mean direct hospital costs increased linearly with CT. The effective radiation dose received by patients with necrotizing pancreatitis is significant. Management changes infrequently follow CT imaging. The ubiquitous use of CT in necrotizing pancreatitis raises substantial public health concerns and mandates a careful reassessment of its utility [123].

EUS

Endoscopic ultrasound (EUS) is one of the fastest growing areas within gastrointestinal endoscopy. Although the growth in the United States has been steady, EUS is exploding in areas of Asia and Eastern Europe. As utilization of EUS is increasing, so is the evolution of the discipline itself. As a result, it is critically important to periodically review the current state of the art. From its inception, EUS has been primarily utilized for staging cancer, assessment of pancreatic disease and evaluation of submucosal lesions. EUS has evolved and is now dominated by the application of EUS-guided fine needle aspiration cytology (EUS-FNA), and the newest emerging application is EUS-guided interventions. The recent literature is a reflection of these trends, with some articles devoted to the standard applications for EUS, but most of the emphasis is on EUS-FNA and EUS-guided interventions [124].

To identify the associated risk factors for hyperechogenic pancreas (HP) which may be observed on endoscopic ultrasound (EUS) and to assess the relationship between HP and obesity. From 2007 to 2007, it was prospectively enrolled 524 consecutive adults who were scheduled to undergo EUS. Patients with a history of pancreatic disease or with hepatobiliary or advanced gastrointestinal cancer were excluded. Finally, 284 patients were included in the analyses. It was further analyzed the risk of HP according to the categories of visceral adipose tissue (VAT) and subcutaneous adipose tissue in 132 patients who underwent abdominal computed tomography scans. On univariate analysis, age older than 60 years, obesity (body mass index $> 25 \text{ kg/m}^2$), fatty liver, diabetes mellitus, hypertension and hypercholesterolemia were identified as significant risk factors associated with HP. On multivariate analysis, fatty liver (OR 2.2), male gender (OR 2.6), age older than 60 years (OR 2.9) and hypertension (OR 2.0) were significantly associated with HP. In the subgroup analysis, VAT was a statistically significant risk factor for HP (OR 5.7, lowest quartile vs highest quartile). It was concluded that hyperechogenic pancreas observed on EUS was associated with fatty liver, male gender, age older than 60 years, hypertension and visceral adipose tissue [125].

CEUS

Contrast-enhanced ultrasound (CEUS) has significantly improved the differentiation of hepatic lesions and the detection of liver metastases. Metastases are usually represented as hypoenhanced areas in the late phase and must then be confirmed histologically. Other lesions presenting hypoenhancement in the late phase are abscesses, hepatocellular and cholangiocellular carcinomas, adenomas, avascular necrosis, haematomas and rarely inflammatory masses. The differentiation between these relies on the patient's history, the number of lesions presenting, the B-image morphology and the enhancement pattern in the early phase of CEUS. It was reported a case of a 49-year-old woman with a in CT assumed pancreatic tumour in whom liver metastases were suspected and investigated by CEUS. In the late phase of this examination hypoenhanced hepatic lesions were observed, prompting us to perform a needle biopsy. The histopathological work-up surprisingly identified the hepatic lesions to be eosinophilic infiltration. After a spontaneous remission it was concluded an allergic reaction to a fluoroquinolone [126].

CT

This was the first in a series of three medical graphics articles featuring the arterial anatomy of the pancreas as depicted on computed tomography images. This arterial anatomy is important in clinical practice because it represents a road map of the routes of tumor spread by ductal adenocarcinoma of the pancreas [127].

MRI

The purpose of one article was to discuss the most current techniques used for pancreatic imaging, highlighting the advantages and disadvantages of state-of-the-art and emerging pulse sequences and their application to pancreatic disease. Given the technologic advances of the past decade, pancreatic MRI protocols have evolved. Most sequences can now be performed in one or a few breath-holds; 3D sequences with thin, contiguous slices offer improved spatial resolution; and better fat and motion suppression allow improved contrast resolution and image quality. The diagnostic potential of MRCP is now almost as good as ERCP, with pancreatic MRI as the main imaging technique to investigate biliopancreatic pain, chronic pancreatitis, and cystic pancreatic tumors at many institutions. In addition, functional information is provided with secretin-enhanced MRCP [128].

To assess the feasibility of multiple-bolus dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) in the pancreas; to optimize the analysis; and to investigate application of the method to a glucose challenge in type 2 diabetes a 4-bolus DCE-MRI protocol was performed on five patients with type 2 diabetes and 11 healthy volunteers during free-breathing. Motion during the dynamic time series was corrected for using a model-driven nonlinear registration. A glucose challenge was administered intravenously between the first and second DCE-MRI acquisition in all patients and in seven of the healthy controls. Image registration improved the reproducibility of the DCE-MRI model parameters across the repeated bolus-acquisitions in the healthy controls with no glucose challenge. Native tissue T1 was significantly lower in patients (374 ± 68 msec) compared with volunteers (519 ± 41 msec) but there was no significant difference in any of the baseline DCE-MRI parameters. No effect of glucose challenge was observed in either the patients or healthy volunteers. It was concluded that multiple bolus DCE-MRI is feasible in the pancreas and is improved by nonlinear image registration but is not sensitive to the effects of an intravenous glucose challenge [129].

MRCP

Magnetic resonance cholangio-pancreatography (MRCP) is a valuable method for the evaluation of biliary and pancreatic diseases and a valuable alternative to endoscopic retrograde cholangiopancreatography (ERCP). It is noninvasive and does not require the use of contrast material or ionizing radiation. Since its introduction in 1991, this technique has significantly improved in spatial resolution, now allowing the accurate assessment of the major bilio-pancreatic diseases. MRCP is commonly performed with heavily T2-weighted sequences in order to highlight static fluids, as those contained in dilated pancreatic and biliary ducts. Newest MR equipments allow to perform MRCP within 10-15 minutes, due to the availability of ultra-fast sequences. Currently, MRCP is widely performed as a primary imaging modality for the assessment of obstructive jaundice and other benign or malignant bilio-pancreatic ducts abnormalities. The primary MRCP application is the evaluation of biliary obstructions due to choledocholithiasis, iatrogenic strictures, cholangiocarcinoma or pancreatic carcinoma. Other MRCP applications include the assessment of the exocrine pancreatic function, following secretin stimulation. Whenever needed, the MRCP may be completed with a conventional contrast-enhanced magnetic resonance imaging (MRI) of the upper abdomen and functional studies as well, thus providing an all-in-one morphological and functional study of the pancreas and biliary system. More recent applications include the possibility of 3D reconstructions and the use of hepato-biliary contrast agent, that provide a higher definition of the biliary tree, both in pathologic and normal conditions. The introduction of 3Tesla magnets could provide higher anatomic details. It was concluded that in the next years the role of MRCP will further expand, due to the availability of faster sequences, 3D imaging and functional studies [130].

PET

Guided biopsy

To establish the feasibility of performing combined positron emission tomography (PET)/computed tomography (CT)-guided biopsy of abdominal masses by using previously acquired PET/CT images registered with intraprocedural CT images 14 patients were reviewed. The patients underwent clinically indicated percutaneous biopsy of abdominal masses (mean size, 3.3 cm; range, 1.2-5.0 cm) in the liver (n=6), presacral soft tissue (n=3), retroperitoneal lymph nodes (n=2), spleen (n=2), and pancreas (n=1). PET/CT images obtained no more than 62 days (mean, 18 days) before the biopsy procedure were registered with intraprocedural CT images by using image registration software. The registered images were used to plan the procedure and help target the masses. The image registrations were technically successful in all but one patient, who had severe scoliosis. The remaining 13 biopsy procedures yielded diagnostic results, which were positive for malignancy in 10 cases and negative in three cases. It was concluded that PET/CT-guided abdominal biopsy with use of prior PET/CT images registered with intraprocedural CT scans is feasible and may be helpful when fluorine 18 fluorodeoxyglucose-avid masses that are not seen sufficiently with nonenhanced CT are sampled at biopsy [131].

As a prognostic factor

One study analyzed the prognostic value of positron emission tomography (PET) for locally advanced pancreas cancer patients undergoing stereotactic body radiotherapy (SBRT). Fifty-five previously untreated, unresectable pancreas cancer patients received a single fraction of 25-Gy SBRT sequentially with gemcitabine-based chemotherapy. On the preradiation PET-CT, the tumor was contoured and the maximum standardized uptake value (SUV_{max}) and metabolic tumor burden (MTB) were calculated using an in-house software application. High-

SUV_{max} and low-SUV_{max} subgroups were created by categorizing patients above or below the median SUV_{max}. The analysis was repeated to form high-MTB and low-MTB subgroups as well as clinically relevant subgroups with SUV_{max} values of <5, 5-10, or >10. Multivariate analysis analyzing SUV_{max}, MTB, age, chemotherapy cycles, and pretreatment carbohydrate antigen (CA)19-9 was performed. For the entire population, median survival was 13 months. Median survival was 10 versus 15 months for the high- and low- SUV_{max} subgroups, which was a statistically significant difference. Similarly, median survival was 10 versus 18 months for the high MTB and low MTB subgroups. When clinical SUV_{max} cutoffs were used, median survival was 6 months in those with SUV_{max} >10, 10 months with SUV_{max} 5.0-10.0, and 18 months in those with SUV_{max} <5. On multivariate analysis, clinical SUV_{max} was an statistically significant independent predictor for overall survival and progression-free survival. It was concluded that PET scan parameters can predict for length of survival in locally advanced pancreas cancer patients [132].

Endoscopy

The role of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) continues to mature. First, minimizing contrast injection of the pancreas, wire-guided cannulation and prophylactic pancreatic stenting have been re-emphasized in recent studies as the most important endoscopic interventions that can lower the risk of post-ERCP pancreatitis. The role of preoperative ERCP in patients with jaundice secondary to pancreatic cancer was raised in a randomized trial; the widespread use of preoperative biliary drainage is now up for debate. The use of ERCP, intraoperative cholangiography, endoscopic ultrasound and magnetic resonance cholangiopancreatography in the evaluation of suspected common bile duct stones is also discussed. Given the risk of complications and development of alternative imaging modalities, diagnostic ERCP is rarely indicated. However, therapeutic ERCP has been bolstered by advances such as fully covered metallic stents and cholangioscopy [133].

Papilla minor appearance at duodenoscopy

The minor papilla serves as a site of alternative pancreatic duct drainage via the accessory pancreatic duct. The objectives of one study were to assess the endoscopic appearance of the minor papilla for characteristics that might predict increased accessory pancreatic duct flow and hence suggest pathology of the downstream pancreatic ductal system. This was a nonrandomized, prospective analysis of consecutively enrolled patients from a US tertiary care medical center. The study cohort consisted of consecutive patients presenting for endoscopic retrograde cholangiopancreatography (ERCP) without prior pancreaticobiliary endotherapy or ductography. Sixty-four patients received a minor papilla score prior to ERCP. A normal pancreatogram was found in 37 of 64 (58 %) patients; the remaining 27 (42 %) patients had an abnormal pancreatogram. The median minor papilla bulge score was 0.49 (range 0-3) in the normal pancreatogram group and 2 (range 0-3) in the abnormal pancreatogram group, which was a statistically significant difference. The median minor papilla orifice score of those with a normal pancreatogram was 0 (range 0-2) compared to 2 (range 0-3) in the abnormal pancreatogram group. The median minor papilla cumulative score of 1 (range 0-5) for the normal pancreatogram group was significantly less than that for the abnormal pancreatogram group (3, range 0-6), resulting in a sensitivity of 96 percent for an abnormal pancreatogram. The minor papilla orifice was noted to be either gaping or actively dripping pancreatic juice in four out of five patients with pancreas divisum. It was concluded that a minor papilla without bulging or a visible orifice would suggest a normal pancreatogram at ERP. Conversely, an abnormal minor papilla, particularly a patent minor papilla orifice, should raise suspicion of pancreatic ductal pathology and can help direct pancreatic endotherapy at the major or minor papillae [134].

Double lumen enteroscopy

Small elevations of pancreatic enzymes are recently recognized complications of double-balloon enteroscopy (DBE). The aim of one study was to check the post-procedure pancreatic enzyme (p-amylase, lipase) levels and to disclose their relationships with technical features of DBE. Peroral (48) and peranal (8) DBEs were performed in 56 patients, and the p-amylase and lipase levels were measured just before and after the procedure. Patients were also evaluated for abdominal pain after DBE using a visual analog scale (VAS). The route-total duration of the procedure, the total insertion length of the scope, the insertion length where the overtube balloon was inflated for the first time, and the duration between the first and second inflations were also noted. Pancreatitis was observed in 6 of 48 (13 %) peroral DBE patients. A VAS score above 5 at 4 h had a sensitivity of 100 percent and specificity of 96 percent for developing post-DBE pancreatitis. Significant correlations were noted between the levels of pancreatic enzymes after DBE and the total insertion length, duration, and duration between the first and second inflations of the balloon, and an inverse correlation was observed between the levels of these enzymes and insertion length at the first inflation, but an age-sex-adjusted regression analysis only disclosed the duration between the first and second inflations as a significantly independent predictor of post-DBE pancreatitis. It was concluded that hyperamylasemia and hyperlipasemia after double-balloon enteroscopy seems to be a complication of peroral DBE, which might be prevented by reducing the time between the first and second inflations of the overtube balloon [135].

Death after ERCP

More than half a million endoscopic retrograde cholangiopancreatography (ERCP) procedures are performed annually in the United States. The risk of severe complications after ERCP is less than 1 percent; however, autopsy pathologists see a select group of patients having fatality. Thirty-five autopsies were performed after ERCP over a 13-year period. Fourteen of these 35 patients died of ERCP complications. The remaining patients formed the control group. Fatal complications of ERCP included acute pancreatitis (7), sepsis (5), gastrointestinal/biliary perforation (3), bleeding (2), myocardial infarction (2), and cardiac arrhythmia (1). Cancer (14) and chronic pancreatitis (4) were the most reported causes of death in the control group. Median times to death after ERCP in ERCP-related deaths versus controls were 10 and 40 days, respectively. The most common indications for the procedure in ERCP-related deaths were suspected choledocholithiasis and jaundice due to biliary obstruction; in controls, jaundice or biliary obstruction and chronic pancreatitis were more common. Patients having fatal ERCP complications had significantly more cannulations reported as "difficult" (69 % vs 20 %). The Klöppel chronic pancreatitis score was significantly lower (mean, 2.6 vs 6.6), and the percentage of nonfibrotic pancreatic parenchyma was significantly higher (mean, 85 % vs 56 %) in ERCP-related death group versus controls. Although patients rarely die after ERCP, our findings suggest that healthy acinar tissue is a risk factor for ERCP-related death, especially in the setting of difficult cannulation [136].

Self-expandable stents

A 6F endoscopic biliary self-expanding metal stent (SEMS) has been newly introduced for intended simultaneous side-by-side bilateral deployment in hilar malignant obstruction. Sixteen consecutive malignant hilar biliary obstruction patients had endoscopic palliative treatment of malignant biliary obstruction with the Zilver 635 SEMS from 2008 to 2010. Technical/functional success rates, early complications (within 30 days of stent placement), early/late stent occlusion, and biliary reintervention rates were evaluated. A total of 49 Zilver SEMSs were placed in 16 patients (mean age 61 years, 6 men) for Bismuth type II (n=4), III (n=5), and IV (n=7) lesions. Twelve had cholangiocarcinoma, 2 had metastatic colon cancer, 1 had lung cancer, and 1 had pancreatic cancer. The technical success rate was 100

percent. Side-by-side simultaneous bilateral stent deployment was required and was achieved successfully in 10 cases. Additional transpapillary stents were placed for potential future biliary access. The 30-day mortality rate was 0 percent. There were 1 early (6 %) and 3 late (19 %) stent occlusions. Successful overall biliary drainage was 75 percent. It was concluded that malignant hilar biliary obstruction endoscopic palliation with the Zilver 635 SEMS offers acceptable initial feasibility, safety, and efficacy profiles. The current design facilitates smaller bile duct negotiation and more precise intrahepatic placement. Expanding available lengths would allow transpapillary bridged bilateral SEMS placement for future reobstructed biliary access [137].

Occluded stents

Although self-expandable metallic stent (SEMS) has a longer patency than plastic stent (PS) for malignant biliary obstruction, stent occlusion can occur and drainage has to be reestablished in a patient with expected long survival. However, the choices are still controversial among restenting with SEMS, PS, and percutaneous transhepatic biliary drainage (PTBD). One study was designed to determine the efficacy and outcome of PS, SEMS, and PTBD for patients with occluded SEMS. A total of 154 ERCPs with SEMS insertion were performed. The causes of obstructive jaundice were cholangiocarcinoma (n=110), pancreatic cancer (n=41), and metastatic carcinoma (n=3). Thirty-two patients (21 %) with occluded SEMS (uncovered SEMS 22 and covered SEMS 10) were identified. PS, SEMS, and PTBD were used to reestablish drainage in 11, 14, and 7 patients, respectively. The second stent was inserted as stent-in-stent. Patients with less advanced disease were preferably opted to have a second SEMS. The median stent patency of second SEMS (100 days) was significantly longer than PS (60 days) and PTBD (75 days). The median survival time for patients with second SEMS (230 days) was significantly longer than patients with PS (130 days) and PTBD (150 days). Subgroup analysis in hilar obstructions showed no statistical difference in second stent patency and survival between PS and SEMS. Pain that required oral narcotic developed in 71 percent (5/7) of PTBD patients. It was concluded that in general, a second SEMS insertion in occluded SEMS provides a significant longer patency time than PS and PTBD. However, the benefit of SEMS as a second intervention in hilar obstructed patients is still doubtful [184].

Fine needle aspiration biopsy

Biomarker use for pancreatic cancer diagnosis has been impaired by a lack of samples suitable for reliable quantitative RT-PCR (qRT-PCR). Fine needle aspirates (FNAs) from pancreatic masses were studied to define potential causes of RNA degradation and develop methods for accurately measuring gene expression. Samples from 32 patients were studied. RNA degradation was assessed by using a multiplex PCR assay for varying lengths of glyceraldehyde-3-phosphate dehydrogenase, and effects on qRT-PCR were determined by using a 150-bp and a 80-bp amplicon for RPS6. Potential causes of and methods to circumvent RNA degradation were studied by using FNAs from a pancreatic cancer xenograft. RNA extracted from pancreatic mass FNAs was extensively degraded. Fragmentation was related to needle bore diameter and could not be overcome by alterations in aspiration technique. Multiplex PCR for glyceraldehyde-3-phosphate dehydrogenase could distinguish samples that were suitable for qRT-PCR. The use of short PCR amplicons (<100 bp) provided reliable gene expression analysis from FNAs. When appropriate samples were used, the assay was highly reproducible for gene copy number with minimal (about 0.7 % of total) variance. It was concluded that the degraded properties of endoscopic FNAs markedly affect the accuracy of gene expression measurements. A novel approach to designate specimens "informative" for qRT-PCR allowed accurate molecular assessment for the diagnosis of pancreatic diseases [139].

ACUTE PANCREATITIS

The acronym “PANCREAS” stands for Perfusion, Analgesia, Nutrition, Clinical assessment, Radiological assessment, ERCP, Antibiotics, and Surgery for easy remembrance and management in daily medical practice [140]:

Perfusion: Fluid resuscitation to maintain urine output between 0.5 and 1.0 mL/kg/h. Oxygenation in order to keep saturation greater than 95 % in severe pancreatitis

Analgesia: Patient-controlled analgesia or traditional on demand analgesia including opioids

Nutrition: Enteral feeding within 48 hours (plus/minus nasojejunal feeding)

Clinical assessment: BISAP, APACHE II or APACHE-O scores for assessment and triage of cases. Management in high dependency areas or intensive care units according to the severity of the pancreatitis

Radiology: Ultrasonography to detect gallstones, choledocholithiasis and local complications. Contrast enhanced computed tomography (CECT) only after need to determine the degree and extent of necrosis. Percutaneous catheter drainage guided by ultrasound and CECT is helpful in the management of necrosis and also in bridging the time until surgery

ERC(P): To be carried out within 72 hours if cholangitis or severe acute pancreatitis with persistent obstruction exists

Antibiotics: There is little evidence to support the role of prophylactic antibiotics for the prevention of infected necrosis. Empirical antibiotics may be started if infection is suspected. Percutaneous ultrasound or CT-guided aspiration for gram staining and culture sensitivity should orient the choice of antibiotics

Surgery: Multi organ failure with necrosis not responding to conservative management including percutaneous catheter drainage, pseudo-aneurysm of the surrounding vessels with bleeding, infected necrosis, pancreatic abscess and bowel perforation.

Guidelines

Several clinical guidelines exist for acute pancreatitis, with varying recommendations. The aim of one study was to determine the quality of guidelines for acute pancreatitis. A literature search identified relevant guidelines, which were then reviewed to determine their document format and scope and the presence of endorsement by a professional body. The quality of guidelines was determined using the validated Grilli, Shaneyfelt, and AGREE instruments. Twenty-one of the 30 guidelines analyzed were endorsed by professional bodies. Median quality scores were as follows: Grilli, 2; Shaneyfelt, 13; and AGREE, 50. Guideline quality did not improve over time. Guidelines endorsed by a professional body had higher scores than those without official endorsement. Guidelines with tables, a recommendations summary, evidence grading, and audit goals had significantly higher scores than guidelines lacking those features. It was concluded that the many clinical guidelines for acute pancreatitis range widely in quality. Guidelines developed by professional bodies, and those with tables, a recommendations summary, evidence grading, and audit goals, are of higher quality [141].

In a summary of the official guidelines of the Italian Association for the Study of the Pancreas regarding the medical, endoscopic and surgical management of acute pancreatitis it is stated [142]:

- clinical features together with elevation of the plasma concentrations of pancreatic enzymes are the cornerstones of diagnosis (recommendation A).
- contrast-enhanced computed tomography (CT) provides good evidence for the presence of pancreatitis (recommendation C) and it should be carried out 48-72 h after the onset of symptoms in patients with predicted severe pancreatitis.
- severity assessment is essential for the selection of the proper initial treatment in the management of acute pancreatitis (recommendation A) and should be done using the APACHE II score, serum C-reactive protein and CT assessment (recommendation C).
- the etiology of acute pancreatitis should be able to be determined in at least 80% of cases (recommendation B).
- an adequate volume of intravenous fluid should be administered promptly to correct the volume deficit and maintain basal fluid requirements (recommendation A); analgesia is crucial for the correct treatment of the disease (recommendation A).
- enteral feeding is indicated in severe necrotizing pancreatitis and it is better than total parenteral nutrition (recommendation A).
- the use of prophylactic broad-spectrum antibiotics reduces infection rates in CT-proven necrotizing pancreatitis (recommendation A).
- infected pancreatic necrosis in patients with clinical signs and symptoms of sepsis is an indication for intervention, including surgery and radiological drainage (recommendation B).

Epidemiology

Previous observational studies have found an increased risk of acute pancreatitis among type 2 diabetes patients. However, limited information is available on this association and specifically on the role of anti-diabetic treatment. It was therefore aimed to further assess the risk of acute pancreatitis in adult patients with type 2 diabetes. It was performed a population-based case-control analysis nested in a cohort of 85,525 type 2 diabetes patients and 200,000 diabetes-free individuals from the general population using data from The Health Improvement Network (THIN) database. Subjects were followed up to ascertain incident cases of acute pancreatitis. Results: We identified 419 cases of acute pancreatitis, 243 in the general population and 176 in the diabetes cohort. Incidence rates were 30.1 and 54.0 per 100,000 person-years in the general population and the diabetes cohort, respectively. In the cohort analysis the adjusted incidence rate ratio of acute pancreatitis in diabetic patients versus the general population was 1.77 (95 % confidence interval 1.46 to 2.15). The magnitude of this association decreased when adjusting for multiple factors in the nested case-control analysis (adjusted odds ratio 1.37; 95 % confidence interval 0.99 to 1.89). Furthermore, we found that the risk of acute pancreatitis was decreased among insulin treated diabetic patients (adjusted OR 0.35, 95 % confidence interval 0.20 to 0.61). It was concluded that type 2 diabetes may be associated with a slight increase in the risk of acute pancreatitis. It was also found that insulin use in type 2 diabetes might decrease this risk [143].

In Taiwan

To investigate the nationwide epidemiology of acute pancreatitis (AP) in a developing country, with emphasis on the contribution of intensive care patients it was analyzed hospital patients with first-episode AP between 2005 and 2007, based on the claims data of a nationally representative sample of 1,000,000 people enrolled in the Taiwan National Health Insurance program. Severe AP was defined according to a modified Atlanta classification. A total of 1693 patients with AP were identified. Crude and adjusted incidence rates of AP in 2005 were 57 and 43 per 100,000 persons, respectively. The age-specific incidence rates increased continuously with age in women, but showed a bimodal distribution in men. Severe

AP was present in 20 percent of the patients; 47 percent of them received intensive care. The hospital days and charges of those receiving intensive care accounted for 22 percent of the total hospital days and for 41 percent of the total hospital charges of all patients with AP, respectively. Hospital mortality was 2.7 percent, ranging from 0.3 percent in nonsevere cases to 18.9 percent in those requiring intensive care [144].

Pathophysiology

To outline signaling profiles and transmigration capacity of monocytes of patients with severe acute pancreatitis 13 patients with severe acute pancreatitis were investigated. All patients had organ dysfunction (acute respiratory distress syndrome in 12, renal dysfunction in eight). Healthy volunteers served as reference subjects. Phosphorylation of nuclear factor-kappaB and p38, signal transducers and activators of transcription (STATs) 1, 3, 5, and extracellular signal-regulated kinases 1/2 in appropriately stimulated and nonstimulated samples were studied using phospho-specific whole-blood flow cytometry. Monocyte chemotactic protein-1-induced transmigration of monocytes among mononuclear cells obtained by density gradient centrifugation was studied using Transwell cell culture inserts covered with confluent layer of endothelial EA-HY cells. Phosphorylation levels of nuclear factor-kappaB induced by tumor necrosis factor, bacterial lipopolysaccharide, muramyl dipeptide, Escherichia coli, Staphylococcus aureus, and Staphylococcus epidermidis were significantly lower in patients' monocytes than monocytes of healthy reference subjects, whereas mitogen-activated protein kinase p38 phosphorylation levels were normal. Phosphorylation levels induced by interleukin-6 in STAT1 and STAT3 and by combination of phorbol 12-myristate 13-acetate and calcium ionophore A23187 in extracellular signal-regulated kinases 1/2, members of a mitogen-activated protein kinase family, were depressed in patients' monocytes, whereas phosphorylation levels induced by granulocyte-macrophage colony-stimulating factor in STAT5 was normal. In nonstimulated samples, phosphorylation levels were normal. The transmigration percentage of patients' monocytes was significantly lower than that of reference monocytes. The authors concluded that in severe acute pancreatitis, monocytes show impaired nuclear factor kappaB and STAT1 activation, which may increase susceptibility to secondary infections. p38 activation is normal and STAT3 activation is depressed, which may contribute to maintenance of systemic inflammation. Extracellular signal-regulated kinases 1/2 activation is impaired, which may depress monocytes' transmigration and may consequently increase risk of infection. Factors that induce or ameliorate pancreatic injury as well as cellular pathways involved have been examined. Causative or sensitizing factors include refluxed bile acids, hypercalcemia, ethanol, hypertriglyceridemia, and acidosis. In addition, the diabetes drug exendin-4 has been associated with pancreatitis, whereas other drugs may reduce pancreatic injury. The intracellular events that influence disease severity are better understood. Cathepsin-L promotes injury through an antiapoptotic effect, rather than by trypsinogen activation. In addition, specific trypsinogen mutations lead to trypsinogen misfolding, endoplasmic reticulum stress, and injury. Endogenous trypsin inhibitors and upregulation of proteins including Bcl-2, fibroblast growth factor 21, and activated protein C can reduce injury. Immune cells, however, have been shown to increase injury via an antiapoptotic effect. The current findings are critical to understanding how causative factors initiate downstream cellular events resulting in pancreatic injury. Such knowledge will aid in the development of targeted treatments for pancreatitis [145].

Genetics

Acute, acute recurrent, and chronic pancreatitis are inflammatory diseases with multifactorial pathogenic mechanisms. Genetic mutations and polymorphisms have been correlated with

pancreatitis. The aim of one study was to investigate the association of cystic fibrosis transmembrane conductance regulator (CFTR) and serine protease inhibitor Kazal type 1 (SPINK-1) gene mutations and monocyte chemoattractant protein 1 (MCP-1) -2518A/G polymorphism with acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP), and to associate genetic backgrounds with clinical phenotype in these three conditions. One hundred eighteen AP, 64 ARP, 142 CP patients, and 88 normal controls were enrolled consecutively. Serum MCP-1 levels were significantly higher in all patients affected by pancreatic inflammatory diseases. Moreover, it was found a significant over-representation of the MCP-1G allele in ARP patients. It was also found a statistically significant association of CFTR gene mutations with ARP, but not with CP. There was no statistically significant association of ARP or CP with the N34S SPINK-1 gene mutation. Interestingly, 39 of 64 ARP patients (61 %) carried at least one genetic mutation and/or polymorphism. Five of 64 ARP patients had pancreas divisum and four of these five also carried the G allele. Analysis of a comprehensive range of potential susceptibility variants is needed to support modeling of the effects of genes and environment in pancreatitis. As such, beyond gene mutations, the context within which those mutations exist must be considered. In pancreatitis the context includes the inflammatory response, clinical features, and exogenous factors [146].

Serine protease inhibitor Kazal type 1 (SPINK1) gene mutations have been associated with chronic pancreatitis of different etiologies; however, little is known about their role in the pathogenesis of acute pancreatitis (AP). The aim of one study was to study the prevalence of the SPINK1 N34S polymorphism in patients with sentinel and recurrent AP (RAP). Patients with AP were enrolled, and genetic tests were carried out to detect the SPINK1 N34S polymorphism. Subjects without pancreatitis from the North American Pancreatitis Study were used as controls. A total of 188 patients (116 with sentinel acute pancreatitis and 72 with recurrent attacks) and 670 controls were evaluated. The SPINK1 N34S polymorphism was detected in 1 of 232 alleles in patients with sentinel AP, 11 of 144 alleles in patients with RAP, and in 19 of 1340 control alleles. There was no difference in the prevalence of the polymorphism between sentinel attack patients and controls. Patients with the polymorphism were more prone to develop recurrent attacks (odds ratio 19.1, 95 % confidence interval 2.4 to 149.6). This means that SPINK1 N34S polymorphism was not associated with the sentinel AP attack, but it substantially increases the risk of recurrent attacks [147].

Molecular biology

The aims of our study were to determine if polymorphisms in the cyclooxygenase 2 (COX-2) gene is associated with acute pancreatitis (AP) and to evaluate if inflammation risk is associated with specific COX-2 gene haplotypes containing these polymorphisms. The COX-2 genotypes for 7 polymorphisms (rs5275, rs2206593, rs4648262, rs4648261, rs2066826, rs5277, rs2745557) were determined using polymerase chain reaction-restriction fragment length polymorphism analysis in 103 patients with AP and 92 healthy controls. Except for rs5275, the frequencies of COX-2 polymorphisms were both similar in patients with mild or severe pancreatitis, so were in pancreatitis patients and in controls. Only rs5275 was statistically significantly associated with AP risk. The association was seen with rs5275 ($P = 0.03$); specifically, patients carrying the TT genotype in comparison with patients carrying the CC genotype had a significantly lower risk of disease (odds ratio, 1.88; 95% confidence interval, 1.06-3.34). Haplotypes with nucleotide T at the -18491961 position (rs5275) and A at the 184915627 position (rs4648261) of COX-2 promoter seem to increase susceptibility (odds ratio, 2.46; 95 % confidence interval, 1.15 to 5.29), a significant difference. These findings suggest that the rs5275 polymorphism in the 3'-untranslated region of the COX-2 gene may be used as 1 marker for defining the risk of acute pancreatitis [148].

Polyamines

Polyamines are ubiquitous organic cations essential for cellular proliferation and tissue integrity. It has previously been shown that pancreatic polyamine depletion in rats overexpressing the catabolic enzyme, spermidine/spermine N¹-acetyltransferase (SSAT), results in the development of severe acute pancreatitis, and that therapeutic administration of metabolically stable alpha-methylated polyamine analogs protects the animals from pancreatitis-associated mortality. The aim of one study was to elucidate the therapeutic mechanism(s) of alpha-methylspermidine (MeSpd). Methods: The effect of MeSpd on hemostasis and the extent of organ failure were studied in SSAT transgenic rats with either induced pancreatitis or lipopolysaccharide (LPS)-induced coagulopathy. The effect of polyamines on fibrinolysis and coagulation was also studied in vitro. Pancreatitis caused a rapid development of intravascular coagulopathy, as assessed by prolonged coagulation times, decreased plasma fibrinogen level and antithrombin activity, enhanced fibrinolysis, reduced platelet count and presence of schistocytes. Therapeutic administration of MeSpd restored these parameters to almost control levels within 24 h. In vitro, polyamines dose-dependently inhibited fibrinolysis and intrinsic coagulation pathway. In LPS-induced coagulopathy, SSAT transgenic rats were more sensitive to the drug than their syngeneic littermates, and MeSpd-ameliorated LPS-induced coagulation disorders. It was concluded that pancreatitis-associated mortality in SSAT rats is due to coagulopathy that is alleviated by treatment with MeSpd [149].

Bacteriology

Acute pancreatitis occasionally presents as pancreatic abscess with complications like pleural effusion and ascites. There are several pre-disposing factors, the most common being cholelithiasis, alcohol abuse, infective causes, trauma, and metabolic causes such as diabetic ketoacidosis, while some cases are idiopathic. Now it was reported a rare case of acute necrotizing pancreatitis in a 40-year-old male who presented with pain in the abdomen, ascites and left basal pleural effusion. A computerized tomography scan showed findings suggestive of pancreatic necrosis, with abscess formation and free-fluid surrounding area. The aspirated pus sample was processed for Gram staining and culture, which yielded growth of *Prevotella* species in an anaerobic culture. Exploratory laparotomy was performed and intra-abdominal collection drained. Necrosectomy of the distal tail and body of the pancreas was performed. The patient was started on antibiotics and along with supportive treatment, responded well [150].

Diagnostics

Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25 percent, 52 percent, and 80 percent mortality, respectively. Other complications such as pseudocyst formation, pseudoaneurysm formation, or venous thrombosis increase morbidity and mortality to a lesser degree. It was reviewed the computed tomographic findings of complications associated with acute pancreatitis with emphasis on their prognostic significance and impact on clinical management [151].

Early CT

Early computed tomography (CT) (within 4 full days after symptom onset) may be performed to distinguish acute pancreatitis (AP) from other intra-abdominal conditions or to identify early pancreatic necrosis. It was analyzed practice and yield of early CT in patients with an

established clinical diagnosis of AP in a Dutch cohort (EARL study). In a multicenter observational study etiology, disease course, CT timing, Balthazar CT score, and clinical management were evaluated. First documented hospital admissions of 166 patients were analyzed. Etiology was biliary (43 %), unknown (21 %), alcoholic (18 %), post-endoscopic retrograde cholangiopancreatography (11 %), and miscellaneous (7 %). In 89 percent (148/166), the disease course was mild. Out of 18 patients with severe AP, 11 eventually developed (peri)pancreatic necrosis. At least one CT (range 1-12) was performed in 47 percent (78/166) of all patients and in 63 percent (49/78) it was acquired within 4 full days after symptom onset. Practice, timing, and Balthazar CT score of early CTs were not significantly different between mild and severe AP. None of the early CTs showed necrosis and no alternative diagnoses were established. In 90 percent (44/49), clinical management was not altered after early CT. In 10 percent (5/49), prophylactic antibiotics were started, but in absence of necrosis. A CT scan was frequently acquired early in the course of AP, but its yield was low and had no implications with regard to clinical management. It seems prudent that clinicians should be more restrictive in the use of early CT, in particular in mild acute pancreatitis, to prevent unnecessary radiation exposure and to save costs [152].

Trypsinogen-2

In acute pancreatitis, rapid diagnosis and early treatment are of importance for clinical outcome. Urinary trypsinogen-2 has been suggested as a promising diagnostic marker; however, studies using the urinary trypsinogen-2 dipstick test (UTDT) have provided varying results. The study was set to evaluate the use of the UTDT (Actim Pancreatitis; Medix Biochemica, Kauniainen, Finland, Medinor, Roskilde, Denmark) in apparent first attack of acute pancreatitis in daily clinics. Acute pancreatitis was defined as more than a 3-fold increase in plasma amylase levels. It was included 75 patients admitted with acute pancreatitis. Thirty-four patients with acute abdominal pain of causes other than pancreatitis served as a control group. In 58 of 75 patients, the UTDT result was positive, giving a sensitivity of 77 percent (95 % confidence interval 66 % to 86 %). In severe cases, the sensitivity improved to 87percent (95 % confidence interval 69 % to 96 %). In 33 of 34 controls, the test result was negative, giving a specificity of 97 percent (95 % confidence interval 84 % to 100 %). The UTDT thus had a low sensitivity but high specificity. These results do not support the UTDT to replace standard plasma amylase for the diagnosis of apparent first attack of acute pancreatitis [153].

Neutrophil gelatinase-associated lipocalin

About 210,000 new cases of acute pancreatitis (AP) involving reversible inflammation of the pancreas are reported in the United States every year. About one-fourth of all patients with AP go on to develop severe acute pancreatitis (SAP), which, unlike uncomplicated or mild acute pancreatitis (MAP, usually a self-limiting disease), constitutes a life-threatening condition with systemic complications, chiefly multiorgan dysfunction. An early prediction of the severity and outcome of patients with acute pancreatitis (AP) can lead to better treatment regimens for patients with SAP. There is currently no established biomarker for the early diagnosis of SAP. In one study, it was investigated the potential of serum neutrophil gelatinase-associated lipocalin (NGAL) as an early marker to distinguish severe (SAP) from MAP and examine its ability to predict the prognosis of patients with SAP. To check the time kinetics of rise in NGAL during AP, it was quantified NGAL levels in sera from mice with MAP or SAP at various time points (6, 12, 24 and 48 h) using sandwich enzyme-linked immunosorbent assay. NGAL levels were also quantified in serum from 28 MAP and 16 SAP cases and compared with 28 chronic pancreatitis and 30 healthy control samples. Samples collected within 5 days from onset of symptoms were included. The relationship of NGAL levels with survival and multiorgan failure (MOF) in SAP was also examined. Although NGAL levels were significantly higher in mice with both MAP and SAP 6 h after induction (compared to control animals), only mice with SAP exhibited a significant increase in NGAL levels at 24

h. NGAL levels declined at 48 h after induction in animals with both MAP and SAP but did not reach baseline levels. Among patients, mean serum NGAL level was significantly higher in SAP (634 ± 139 ng/ml) compared to MAP (85 ± 7 ng/ml). On subanalysis, the difference between MAP and SAP cases was significant in the first 48 h but not at 72, 96, or 120 h:

	48 h	72 h	96 h	120 h
Specificity	100 %	96 %	97 %	84 %
Sensitivity	100 %	88 %	92 %	94 %

NGAL levels were significantly higher in SAP cases complicated by MOF, and high NGAL levels in SAP appeared to correlate with a fatal outcome. It was concluded that data provide the first evidence for the potential of serum NGAL as an early marker to distinguish MAP from SAP. Further, high NGAL levels predict MOF and fatal outcome in patients with SAP [154].

Prediction of severity

Current methods to predict the development of severe pancreatitis are complex, cumbersome, and inaccurate. Simpler scoring systems like the one studied in this issue of the Journal are an improvement in simplicity but not in accuracy. More sophisticated approaches are needed for more accurate prediction, which would allow improved triage and management of these patients [155].

ESR an CRP

To investigate the performance of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for predicting severe acute pancreatitis (AP). Methods: Fifty patients with AP were prospectively enrolled. Erythrocyte sedimentation rate and CRP were measured at admission and every 12 hours for 48 hours after admission. Thirty percent of the patients developed severe AP. Patients with severe AP had higher levels of ESR (77 ± 5 vs 50 ± 5 mm/h) and CRP (218 ± 31 vs 97 ± 12.1 mg/L) at 36 hours after admission compared with those with mild AP. Erythrocyte sedimentation rates of 60 mm/h or greater predict severe AP at 36 hours with a sensitivity, specificity, and positive and negative predictive values of 86 percent, 57 percent, and 48 percent and 90 percent, whereas CRP of 150 mg/L or greater provided the results of 86 percent, 87 percent, and 75 percent and 93 percent, respectively. Elevation of either ESR or CRP at 24 hours increased the sensitivity and negative predictive value to 100 percent, and elevation of both ESR and CRP increased the specificity and PPV to 100 percent. It was concluded that erythrocyte sedimentation rate can predict severe AP with a slightly inferior performance to CRP. Combined ESR and CRP at 24 hours can predict severe AP accurately [156].

Bedside index for severity in acute pancreatitis

Identification of patients at risk for severe disease early in the course of acute pancreatitis is an important step to guiding management and improving outcomes. A new prognostic scoring system, the bedside index for severity in AP (BISAP), has been proposed as an accurate method for early identification of patients at risk for in-hospital mortality. The aim of this study was to compare BISAP (blood urea nitrogen >25 mg/dl, impaired mental status, systemic inflammatory response syndrome (SIRS), age>60 years, and pleural effusions) with the "traditional" multifactorial scoring systems: Ranson's, Acute Physiology and Chronic Health Examination (APACHE)-II, and computed tomography severity index (CTSI) in predicting severity, pancreatic necrosis, and mortality in a prospective cohort of patients with

AP. Extensive demographic, radiographic, and laboratory data from consecutive patients with AP admitted or transferred to our institution was collected between 2003 and 2007. The BISAP and APACHE-II scores were calculated using data from the first 24 h from admission. Predictive accuracy of the scoring systems was measured by the area under the receiver-operating curve (AUC). There were 185 patients with AP (mean age 52, 51 % males), of which 73 percent underwent contrast-enhanced CT scan. Forty patients developed organ failure and were classified as severe AP (22 %). Thirty-six developed pancreatic necrosis (19 %), and 7 died (mortality 3.8 %). The number of patients with a BISAP score of ≥ 3 was 26; Ranson's ≥ 3 was 47, APACHE-II ≥ 8 was 66, and CTSI ≥ 3 was 59. Of the seven patients that died, one had a BISAP score of 1, two had a score of 2, and four had a score of 3. AUCs for BISAP, Ranson's, APACHE-II, and CTSI in predicting SAP are 0.81 (confidence interval (CI) 0.74 to 0.87), 0.94 (CI 0.89 to 0.97), 0.78 (CI 0.71 to 0.84), and 0.84 (CI 0.76 to 0.89), respectively. It was thus confirmed that the BISAP score is an accurate means for risk stratification in patients with acute pancreatitis. Its components are clinically relevant and easy to obtain. The prognostic accuracy of BISAP is similar to those of the other scoring systems. It was concluded that simple scoring systems may have reached their maximal utility and novel models are needed to further improve predictive accuracy [157].

POF and MOF

Persistent and multiple organ failure (POF and MOF) are predictive of death in acute pancreatitis (AP). Local complications without organ failure are associated with morbidity but a low risk of mortality. It was aimed to design a three-category classification of AP severity and to compare it with the Atlanta Classification in terms of morbidity and mortality. Severe AP was defined as death, POF (>48 h) or MOF. Moderate AP was defined as the presence of acute collections and/or pancreatic necrosis. Mild AP was defined by exclusion. It was compared this classification with AC in 144 episodes of AP. In the three-category classification, severe AP was associated with significantly more frequent intensive care unit admission, invasive treatment and mortality than moderate and mild AP. Severe AP patients required longer hospital stay and more nutritional support than mild AP patients. Patients with moderate AP had significantly longer hospital stay and more need for nutritional support than patients with mild AP. Five patients died, all of them with MOF and/or POF. Conclusions: A three-category classification distinguishes three homogeneous groups of severity [158].

APACHE

Multifactor scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, are useful for predicting the severity of acute pancreatitis. However, they are rather complicated. The aim of one study was to introduce renal rim grade (RRG) as a severity assessment measure for acute pancreatitis. One hundred twenty-two eligible acute pancreatitis patients who underwent abdominal computed tomography on admission were evaluated for RRG (grades 1-3). The end points were the severity of illness and hospital mortality. Furthermore, RRG was compared with the Balthazar score, the CT severity index, the Ranson score, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score, using a receiver operating characteristic analysis. The exacerbation rates into severe disease were 3 percent (grade 1), 4 percent (grade 2), and 89 percent (grade 3). The mortality rates were 3 percent (grade 1), 8 percent (grade 2), and 31 percent (grade 3). The area under the receiver operating characteristic curves to predict the severe disease and mortality using the RRG system were comparable with other scoring systems [159].

The primary aim of one study was therefore to analyze the conventional clinical data and parameters within 24 hours after admission of 338 patients with severe acute pancreatitis, particularly the effect of C-reactive protein (CRP), albumin (ALB), and total cholesterol (TC).

The overall inhospital mortality rate was 8 percent (28/338). The mean time from hospital admission to death was 29 days (range, 9-47 days). Multivariate analysis indicated that the inhospital mortality increased significantly more than 7-fold higher in patients with severe hypoalbuminemia (ALB < 30 g/L). The CRP levels exceeding 170 mg/L were significantly associated with a 7-fold inhospital death. A serum TC level between 4.37 and 5.23 mmol/L had significant protective effect. Total cholesterol levels exceeding 5.23 mmol/L were risk factors to predict inhospital mortality with no significant difference. The strongest prognostic factor was serum ALB [160].

Other scoring systems

It was evaluated contemporary organ dysfunction scoring systems for early prediction of severity in acute pancreatitis (AP) in a consecutive cohort of 181 patients with AP where organ dysfunction scores (logistic organ dysfunction system, LODS) score, Marshall organ dysfunction score, and sequential organ failure assessment score) were collected at 24 and 48 hours. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated on admission and 24 and 48 hours and C-reactive protein level measured at 48 hours. Patients who died or used critical care facilities (level 2/3) during admission were classed as severe. Area under curve for APACHE II score at admission was 0.78 (95 % confidence interval 0.69 to 0.86). At 24 hours, area under curve for LODS, Marshall organ dysfunction system, sequential organ failure assessment, and APACHE II scores were 0.82, 0.80, 0.80, and 0.82, respectively. The LODS score at cutoff of 1 achieved 90 percent sensitivity and 69 percent specificity, corresponding to a positive predictive value of 38 percent. Acute Physiology and Chronic Health Evaluation II score as a rule-out for selection of mild cases at a test threshold of 9 (scores ≤ 8 being selected) gives homogeneity of 91 percent and efficiency of 79 percent. It was concluded that contemporary organ dysfunction scoring systems provides an objective guide to stratification of management, but there is no perfect score. All scores evaluated performed equivalently at 24 hours. Acute Physiology and Chronic Health Evaluation II may have practical clinical value as a rule-out test [161].

To study the correlation between established magnetic resonance (MR) imaging criteria of disease severity in acute pancreatitis and the Acute Physiology And Chronic Healthy Evaluation II (APACHE II) score, and to assess the utility of each prognostic indicators in acute pancreatitis. In the study there were 94 patients with acute pancreatitis (AP), all had abdominal MR imaging. MR findings were categorized into edematous and necrotizing AP and graded according to the MR severity index (MRSI). The APACHE II score was calculated within 24 h of admission, and local complications, death, duration of hospitalization and ICU were recorded. Statistical analysis was performed to determine their correlation. In patients with pancreatitis, no significant correlation can be found between the APACHE II score and the MRSI score. The MRSI score correlated well with morbidity but not with mortality. The APACHE II score correlated well with mortality but not with the morbidity. The MRSI score was superior to the APACHE II score as a predictor of the length of hospitalization. A high MRSI and APACHE II score correlated with the need for being in the intensive care unit (ICU). It was concluded that in patients with pancreatitis, MRSI is superior to APACHE II in assessing local complications from pancreatitis but has a limited role in determining systemic complications in which the APACHE II score excels [162].

To evaluate contemporary organ dysfunction scoring systems for early prediction of severity in acute pancreatitis (AP) in a consecutive cohort of 181 patients with AP, organ dysfunction scores (logistic organ dysfunction system [LODS] score, Marshall organ dysfunction score, and sequential organ failure assessment score) were collected at 24 and 48 hours. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated on admission and 24 and 48 hours and C-reactive protein level measured at 48 hours. Patients who died or used critical care facilities (level 2/3) during admission were classed as severe. Area under curve for APACHE II score at admission was 0.78 (95 % confidence interval 0.69

to 0.86). At 24 hours, area under curve for LODS, Marshall organ dysfunction system, sequential organ failure assessment, and APACHE II scores were 0.82, 0.80, 0.80, and 0.82, respectively. The LODS score at cutoff of 1 achieved 90 percent sensitivity and 69 percent specificity, corresponding to a positive predictive value of 38 percent. Acute Physiology and Chronic Health Evaluation II score as a rule-out for selection of mild cases at a test threshold of 9 (scores ≤ 8 being selected) gives homogeneity of 91 percent and efficiency of 79 percent. It was concluded that contemporary organ dysfunction scoring systems provides an objective guide to stratification of management, but there is no perfect score. All scores evaluated here perform equivalently at 24 hours. Acute Physiology and Chronic Health Evaluation II may have practical clinical value as a rule-out test [163].

Protein C

Protein C modulates microvascular thrombosis in sepsis, with levels being depleted in severe cases. Similar changes occur in necrotizing acute pancreatitis (AP). However, little is known of the pathophysiological characteristics of endogenous protein C early in the disease course of AP. One study undertook an evaluation of protein C levels in AP. In a consecutive series of 57 patients with AP, the chromogenic substrate method was used to determine functional protein C levels in plasma. Protein C activity and variables required for the calculation of Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were assessed at admission and 24 and 48 hours after admission. Results: The median functional protein C level was 97 U/dL (range, 41-178 U/dL) on admission and 96 U/dL (range, 46-170 U/dL) 24 hours after admission. There was no significant difference in the functional protein C levels between the patients with an admission APACHE score of 8 or higher and those with lower APACHE II scores. Linear regression plots showed a nonsignificant trend to the lower levels of functional protein C activity in those patients with higher APACHE II scores. It was concluded that in human acute pancreatitis, functional protein C levels are conserved in mild disease. However, there is evidence that levels are depleted early in severe disease, suggesting a parallel between the pathophysiology of severe sepsis and that of severe AP [164].

Intestinal fatty acid binding protein (I-FABP)

To study the use of intestinal fatty acid binding protein (I-FABP) in diagnosing gut dysfunction in patients with acute pancreatitis (AP) 32 patients with AP onset within 7 days were enrolled in a study. The severity of disease and the gut dysfunction were evaluated as follows: on admission, on the seventh day of disease attack, and on the third day after enteral nutrition. Serum levels of I-FABP, citrulline, and C-reactive protein (CRP) and the lactulose and mannitol absorption ratio in urine were measured in parallel. Results: The serum level of I-FABP increased on admission, and it was more pronounced in severe attacks. All patients had increased gut dysfunction score, serum level of CRP, and urine level of lactulose and mannitol absorption ratio with decreased serum level of citrulline. A positive correlation was found between the following pairs of measurement on admission: serum level of I-FABP and gut dysfunction score, serum level of I-FABP and Acute Physiology and Chronic Health Evaluation II score, I-FABP and serum level of CRP, and serum level of I-FABP and the length of ICU stay. A reverse correlation between the serum level of I-FABP and the serum level of citrulline was found. The authors concluded that the serum level of I-FABP can be used for assessing the gut dysfunction and disease severity of AP [165].

Interleukins

The early identification of patients at risk for severe acute pancreatitis is crucial. Serum markers of disease severity have been assessed including interleukin (IL)-6 and IL-8; however, their predictive accuracy has varied significantly across studies. It was conducted a

meta-analysis to assess the accuracy of IL-6 and IL-8 at predicting severe acute pancreatitis. It was identified relevant published articles and calculated pooled sensitivities, specificities and likelihood ratios using the random-effect model. It was included values for days 1, 2 and 3 of presentation for IL-6 and for days 1 and 2 for IL-8. It was also constructed summary receiver-operating curves and assessed the area under the curve (AUC) and the diagnostic odds ratios (DORs) as measures of diagnostic accuracy. For IL-6, it was included 7 reports for day 1 and 4 reports for days 2 and 3. For IL-8, it was analyzed 5 studies for day 1 and 4 for day 2. The pooled IL-6 sensitivities ranged between 81 and 84 percent and specificities between 76 and 85 percent with positive likelihood ratios of 3.43, 4.90 and 4.40 for days 1, 2 and 3, respectively. The IL-8 pooled sensitivities were 66 and 71 percent with specificities of 67 and 91 percent for days 1 and 2 with positive likelihood ratios of 1.96 and 8.15. The IL-6 AUCs were 0.75, 0.88 and 0.85 for days 1, 2 and 3. The IL-8 AUCs were 0.73 and 0.91 for days 1 and 2. The DOR for IL-6 was higher than that of IL-8 on day 1. It was concluded that IL-6 and IL-8 seem to perform at an acceptable level in predicting severe acute pancreatitis. Larger confirmatory studies formally comparing this performance with that of more commonly used markers are needed [166].

Acute pancreatitis (AP) is a severe inflammatory disease with high mortality and morbidity rates. It has previously been demonstrated that resistin may represent an early marker of inflammation in AP. It was also revealed that ghrelin may have anti-inflammatory potential. However, the role of adipohormones in AP-resistin and ghrelin as well as the proinflammatory cytokine interleukin (IL)-18 has not yet been fully elucidated. The study group comprised 32 patients with alcoholic AP and 30 controls matched for age, sex, and body mass index (BMI). In all cases AP was classified as grade C according to Balthazar's computed tomography (CT) score and as severe (3 points) according to Ranson's criteria. Serum levels of resistin, ghrelin, and IL-18 were measured on first, third, and fifth day of hospitalization by enzyme-linked immunosorbent assay (ELISA). On first day of hospitalization the mean serum resistin concentration in AP patients was significantly higher than in controls and further increased on third and fifth day of hospitalization (17 ± 4 ng/mL and 26 ± 8 ng/mL, respectively). On first day of hospitalization the mean serum IL-18 concentration in AP patients was significantly higher than in controls, on third day its level further increased, and on fifth day it decreased to a level similar to that observed on admission. The serum ghrelin concentrations on first, third, and fifth day of hospitalization were comparable, and significantly higher than in controls. Significant correlation between C-reactive protein (CRP) and resistin levels and between CRP and IL-18 on day of admission was found. It was concluded that serum concentration of IL-18 and resistin may contribute to inflammatory response and may be useful as an early marker of inflammation in AP [167].

Refeeding in mild acute pancreatitis

The aim of one study was to compare two protocols regarding the initiation of oral nutrition in patients with mild acute pancreatitis. It was randomized 143 patients to the Lipase directed (LIP) (n=74) and the self selected PAT (n=69) group. In the (PAT) group, the patients restarted eating through self-selection. In the LIP group, serum lipase had to normalize before eating. The mean time between admission and oral nutrition was 2 days (interquartile range, IQR, 1-3) in the PAT group and 3 days (IQR, 2-4) in the LIP group, which was a significant difference. Before and after the first meal, the mean visual analogue scale (VAS) was $3.14 \text{ mm} \pm 11.5 \text{ mm}$ in the PAT group and $2.85 \text{ mm} \pm 1.64$ in the LIP group. The length of hospital stay was 7 days (median; IQR, 5-11) in the PAT group and 8 days (median; IQR, 6-12) in the LIP group. It was concluded that it was not possible to demonstrate a difference in postprandial abdominal pain or in the length of hospital stay. Patients with self-selected eating, however, were able to restart eating 1 day earlier, and this difference was found to be

significant. The data shows that normalization of serum lipase is not obligatory for enteral nutrition in mild acute pancreatitis [168].

Risk of readmission

Reducing rapid readmission of patients to the hospital following discharge could improve quality of treatment and reduce costs. Little is known about clinical predictors of early readmission for acute pancreatitis (AP). It was developed a strategy to identify and stratify patients with AP at risk for readmission within 30 days of discharge. It was derived and validated a model in a cohort of patients hospitalized with AP from 2005 to 2009. Early readmission was defined as admission to the hospital or re-evaluation in the emergency department within 30 days of discharge. The cohort was divided into a derivation cohort (admitted 2005- 2007, n=248) and a validation cohort (admitted 2008- 2009, n=198). A weighted scoring system was developed using logistic regression for the prediction of early readmission. Accuracy was assessed by area under the receiver-operator characteristic (ROC) curve analysis. Of the total patients, 21 percent (92/446) had early readmission. Multivariable analysis identified the following discharge characteristics as independent risk factors for early readmission: gastrointestinal symptoms, eating less than a solid diet, pancreatic necrosis, treatment with antibiotics, and pain. Weighted risk scores stratified patients into groups of low, moderate and high risk for early readmission: 4 percent, 15 percent and 87 percent, respectively, in the derivation set and 5 percent, 18 percent and 68 percent, respectively, in the validation set. Area under the ROC curve indicated this score was an accurate predictor. It was thus created a scoring system that accurately predicts which patients with AP have high and low risk of readmission to the hospital within 30 days of discharge [169].

Early unplanned readmission is a potential target for quality improvement and cost reduction. The aims of one study were to determine the frequency of early readmission following hospitalization for acute pancreatitis (AP) and identify risk factors for early readmission in patients hospitalized for AP. A retrospective, observational cohort study was performed including all inpatients with AP at a tertiary-care hospital between 2005 and 2007. Early readmission was defined as admission to the hospital or reevaluation in the emergency department within 30 days of discharge. It was analyzed demographics, etiology, markers of severity (according to Atlanta symposium), comorbidities, complications, therapeutic interventions, and discharge symptoms as potential risk factors for readmission. There were a total of 248 patients discharged with AP during the study period, of whom 19% (47/248) had an early readmission. Median time to readmission was 9 days (interquartile range, 5-15). Median rehospitalization length of stay was 4 days (3-8). In multivariate analysis, the strongest risk factors for early readmission included gastrointestinal symptoms (nausea, vomiting, or diarrhea) at discharge (odds ratio (OR) 44.2; 95 % confidence interval 4.1 to 472); discharge on less than a solid diet (OR 23.8; 95 % confidence interval 4.8 to 118); and moderate to heavy alcohol use (OR 10.1; 95 % confidence interval 1.2 to 82.6) [170].

Mannometry in idiopathic recurrent pancreatitis

Ten to 30 percent of patients with pancreatitis are classified as idiopathic after the initial evaluation. The aim of one study was to assess the diagnostic yield of endoscopic retrograde cholangiopancreatography (ERCP) and sphincter of Oddi manometry in patients with idiopathic pancreatitis in a tertiary referral center. A single-center, retrospective study analyzing the ERCP and manometry results of 1,241 patients who were classified as having idiopathic pancreatitis based upon their initial evaluation. A single episode of pancreatitis occurred in 20 percent, acute recurrent pancreatitis in 56 percent and chronic pancreatitis in

23 percent of the patients undergoing ERCP. Sphincter of Oddi dysfunction was found in 40 percent and pancreas divisum in 19 percent of the patients. Biliary stone disease was found in 3 percent. Intraductal papillary mucinous neoplasms were identified in 52 patients with increasing frequency in older age groups. The overall diagnostic yield of ERCP and sphincter of Oddi manometry to elucidate a potential cause of pancreatitis was 66 percent. Of these, 92 percent of patients had findings amenable to endoscopic therapy. The complication rate was 12 percent. The authors concluded that in this large series, ERCP with manometry frequently identified conditions which probably caused or contributed to the idiopathic pancreatitis. Long-term studies are awaited to determine outcomes after correctable factors are addressed [171].

Clinical aspects of pain in acute pancreatitis

Pain in acute pancreatitis is often of sudden onset with excruciatingly severe pain or may be a more gradual onset with moderate abdominal pain several hours after a large meal. There are also reported cases of acute pancreatitis without pain, but these are rare – or at least rarely diagnosed. Mild, alcohol-induced pancreatitis is sometimes recognized by the patient not until “the day after the day after” – when all other symptoms related to hangover have resolved – which means that pancreatitis pain was obscured by alcohol confusion when it was at its peak. According to some authors, there can be some localization of the pain depending on the part of the pancreas that is most severely affected by the inflammation. Painful stimuli in the head of the pancreas may thus be perceived as pain in the right upper abdominal quadrant; there is a radiation from the body of the pancreas to the epigastrium, and from the tail to the left upper quadrant and shoulder. However, pain is localized to the epigastrium and periumbilical regions in about two thirds of the patients, whereas in most other cases, pain is diffuse and difficult to localize for the patient. This is probably due to general pancreatitis and a peripancreatic retropancreatic edema and inflammation. About one third of the patients report that the pain is radiating to the back. The pain is often continuous for hours (e.g. biliary pancreatitis) or days (alcoholic pancreatitis and more severe forms of biliary pancreatitis), but can be intermittent in less than 15 percent of patients. The intensity is reported from “as severe as possible” to “well tolerable.” In most cases, a patient will require potent analgesic for treatment. However, there is little correlation between the severity of pancreatitis and the severity of pain and its localization. In most severe cases of pancreatitis the patient may already be in shock or preshock when admitted to the emergency ward, which means that the patient will not express pain as his or her leading complaint or may not even experience pain at all. Absence of pain in a severely ill patient with acute pancreatitis is an ominous sign [172].

There seems to be no single cause of pain in acute pancreatitis, but several factors contribute. Pain can be due to the inflammation with direct inflammatory stimulation of pancreatic and peripancreatic nerve endings and the production of noxious and pain-inducing substances in the sensitive peritoneum. This is likely to be a local process as most patients with acute pancreatitis have localized pain in the epigastrium and the surrounding upper part of the abdomen. On the other hand, as patients can also have pain in the back, this may represent neural referred pain, or spread of noxious stimuli through a large part of the upper retroperitoneum. The swelling of the gland is unlikely to cause intrapancreatic pain as there are few sensory nerves inside the pancreas (if any), but the pressure effects on the surrounding tissues may well be generating pain. However, there is no demonstrable correlation between pain and the size or grade of pancreatic swelling and no correlation with compression or distension of the biliary tract, duodenum, or pancreatic “capsule” by an inflammatory mass, or by pseudocysts. Hypertension within the ducts due to obstruction has not been shown to be generally present in acute pancreatitis. There is probably relative ischemia of the pancreatic gland at some point of the inflammation and a low pH, but

whether this is of significance for pain sensations is not known. At present it is probable correct to assume that the origin of pain in acute pancreatitis is multifactorial, and more research is needed to clarify which cause or causes of pain are most important and most likely to benefit from intervention. However, compared to other questions regarding the pathophysiology of acute pancreatitis, the answer has presently little impact on the choice of pain medication and has therefore attracted limited attention from researchers. From the patients' point of view here are already several acceptable options for treatment of pain in acute pancreatitis [172].

Randomized study on pain in acute pancreatitis

Acute pancreatitis is commonly associated with severe abdominal pain, making early pain relief a primary goal of the treatment. This study was undertaken to assess the efficacy of a continuous intravenous infusion of procaine compared with that of a placebo infusion in providing pain relief in patients with acute pancreatitis. Forty-two patients with acute pancreatitis were prospectively randomized to receive, in a double-blind setting, a continuous i.v. infusion of a 1 percent solution of procaine (procaine group) or placebo (placebo group, receiving a 0.9 % saline solution) on the first three days of treatment in a hospital setting. The maximal infusion rate of the procaine solution was 8 mL/h, i.e. 1.92 g/24 h. The rate and total amount of infused fluid was similar in the placebo group. Additionally buprenorphine (Temgesic, sublingual [s.l.]) were given on demand for additional pain relief. The gender ratio and the severity of the pancreatitis (APACHE II score, Ranson score) were comparable between the two groups, while the patients of the control group were eight years older. The i.v. infusion of procaine did not reduce the demand for buprenorphine in the procaine group and was similar to that in the placebo group. Furthermore, explorative data analysis revealed that patients of the procaine group had higher bodily discomfort and nausea scores and also tended to feel more pain than the patients of the placebo group. These data do not indicate a clinically meaningful analgesic effect of i.v. infusion of procaine (maximal amount. 1.92 g/24h) in patients with acute pancreatitis, but suggested that this infusion actually increased the feeling of bodily discomfort and nausea. It was thus concluded that a constant i.v. infusion of procaine should no longer be recommended for pain relief in patients with acute pancreatitis anymore [173].

Gallstone-induced pancreatitis

There are three main goals of imaging: the diagnosis of acute pancreatitis when there is doubt after clinical examination and initial laboratory testing, the detection of local complications in patients with severe disease, and the definition of the cause of pancreatitis (i.e. detection of gallstones or structural anomalies such as intraductal obstruction due to benign or malignant tumours). Diagnosis of gallstone pancreatitis has three components. The first indication of a possible biliary cause for acute pancreatitis is the presence of risk factors of gallstones. The second step is biochemical detection of raised plasma aminotransferases. The third step is to ensure appropriate timing of diagnostic imaging, and to choose the most suitable imaging technique, for the detection of gallstones, particularly stones within the bile duct. This choice is not clearly defined and has been controversial. Some techniques such as ERCP with sphincterotomy may be therapeutic as well as diagnostic, which has added to the confusion. In this review, we focus firstly on techniques to achieve early diagnosis of gallstones, in order to plan intervention, and secondly on methods to detect bile duct stones in a patient with gallbladder stones. International guidelines recommend prompt treatment of gallstones if they are detected, ideally with definitive treatment before the patient leaves hospital. Therefore, it is necessary to have an easily accessible and effective modality for diagnosis of gallstones soon after presentation with the first attack of pancreatitis. Any patient with acute pancreatitis who has evidence of gallbladder stones should be considered

to have gallstone-associated pancreatitis, because a causative link and the risk of recurrence cannot be excluded in these patients. It is not necessary to demonstrate stones in the bile duct as the causative stone may have passed through the sphincter, and the migration of further stones from the gallbladder may be sufficient to trigger a subsequent episode. On admission to hospital the diagnosis of gallstones may be made from the history of a previous cholecystectomy or previous demonstration of gallstones. However, due to the prevalence of gallbladder stones in the general population, physicians should pay attention to atypical signs that suggest another etiology (e.g. weight loss, pancreatic and biliary duct dilation) and look for other signs of stone migration to support the diagnosis. Early (<48 h after clinical onset) and repeated estimation of plasma aminotransferases is essential. A peak with rapid resolution is strong evidence for a biliary cause. Alkaline phosphatase and bilirubin are less helpful. Elevation of serum transaminases has positive predictive values ranging from 83 to 87 percent, although sensitivity was less good and a negative predictive value was unreliable. A cutoff of transaminase at twice normal gives sensitivity and specificity of 74 and 84 percent. Ultrasonography is the gold standard for diagnosis of gallstones in the gallbladder. It is non-invasive, safe, cheap, repeatable and widely available. The sensitivity of ultrasonography for gallstones is >90 percent in the acute situation, and >95 percent when symptoms have resolved. Accordingly it is recommended that if the initial ultrasound examination is negative and there is a suspicion of gallstones from the history or biochemical tests, the ultrasound scan should be repeated under optimal conditions (patient free of pain, fasted overnight, scan performed by an experienced sonographer) in order to confidently exclude gallstones. Ultrasonography of the gallbladder should be performed within 24 h of admission because this will allow planning of early intervention, particularly endoscopic sphincterotomy, if the patient is unwell with evidence of cholangitis, and will allow the planning of definitive treatment of gallstones by either laparoscopic cholecystectomy or elective endoscopic sphincterotomy when the patient has recovered from the acute episode, but before discharge from hospital. Another argument for early ultrasonography is that after a long period of fasting, the interpretation of the presence of biliary sludge and even of gallbladder stones may be difficult, as many patients will have biliary stones after a prolonged illness such as severe pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) is now well established for the detection of bile duct stones. It has the advantage that it is non-invasive and quick to perform. MRCP will detect bile duct stones with a sensitivity between 91 and 100 percent and an accuracy between 92 and 97 percent. The limit of detection is about 1 mm and stones smaller than 5 mm may be overlooked. It has been demonstrated that MRCP had very similar sensitivity and accuracy to operative cholangiography for the detection of bile duct stones, and it is reasonable to include MRCP in the diagnostic algorithm as an alternative to operative cholangiography. However, MRCP will add nothing in patients scheduled for endoscopic sphincterotomy as sole treatment; these patients will require intervention to prevent future attacks from stone migration, rather than to clear the bile duct. MRCP has the advantage that it can demonstrate the anatomy of the bile duct and pancreatic ducts reliably and non-invasively. This enables exclusion of an anatomical cause of pancreatitis, such as a tumoral obstruction, in particular, intraductal papillary mucinous neoplasm. Further functional information may be added if secretin is given at the time of MRCP. If the clinical context strongly suggests that pancreatitis has been caused by stone migration but repeated ultrasonography performed by senior radiologists does not confirm this, endoscopic ultrasonography should be performed (as soon as the condition of the patient is suitable). Endoscopic ultrasound (EUS) is probably the most sensitive means of detecting microlithiasis and confirming a biliary cause of pancreatitis. EUS is more reliable for the detection of stones in the gallbladder than a single ultrasound examination. Transabdominal ultrasound is notoriously unreliable for the detection of bile duct stones whereas EUS has 95 percent sensitivity. Microlithiasis is said to be present in between 40 and 80% of idiopathic acute pancreatitis. If stones have not been detected on transabdominal ultrasound, and particularly if the transaminase values were raised during the acute phase, EUS will demonstrate microlithiasis with sensitivity and specificity between 90 and 100 percent. Considering the high sensitivity of EUS in this setting, a patient who

experienced one or several episodes of so-called idiopathic acute pancreatitis in whom EUS does not show gallbladder lithiasis should not undergo cholecystectomy. Most patients with acute pancreatitis recover spontaneously without intervention. However, if gallstones caused the pancreatitis there is an ever-present risk that passage of a second stone will cause another, potentially fatal, attack. Definitive management of the gallstones should aim to prevent a recurrence of pancreatitis. For most patients this will mean laparoscopic cholecystectomy to remove the source of further stones with the lowest risk of exacerbation of pancreatitis or procedure-induced haemorrhage. All patients who undergo laparoscopic cholecystectomy should have an adequate cholangiogram to confirm the presence or absence of stones in the bile duct. This is usually done by intra-operative cholangiography, but some centres prefer a pre-operative cholangiogram by MRCP. When cholangiography is performed more than 4 or 5 days after the onset of symptoms, the risk of finding a bile duct stone is 10 percent or less. Accordingly, an operative cholangiogram at this time will show a normal bile duct in approximately 90 percent of patients with gallstone pancreatitis, and these patients will avoid the risks associated with endoscopic sphincterotomy. This timing also has the advantage that the initial acute inflammatory response will have settled, and the risk of exacerbating the inflammatory reaction will have passed. If stones are found at operation they can be managed either by laparoscopic bile duct exploration in appropriate cases or by subsequent endoscopic sphincterotomy. If the postoperative endoscopic approach is chosen, placement of a transcystic catheter at cholecystectomy facilitates subsequent management. If there is doubt about the presence of a stone in the duct, a further confirmatory cholangiogram may be obtained before proceeding to sphincterotomy, and if there is difficulty cannulating the papilla, a guidewire may be passed through the catheter to ensure cannulation by the rendezvous technique and allow safe sphincterotomy. Alternatively, patients with gallstone pancreatitis may be managed definitively by endoscopic sphincterotomy. This approach carries a well-recognised risk between 5 and 10 percent of exacerbation of the pancreatitis, and of sphincterotomy bleeding. However, pancreatic duct stenting may reduce the risk of pancreatitis. Endoscopic sphincterotomy may be appropriate in patients in whom there is co-morbidity, which increases the risks of general anaesthesia for cholecystectomy. In particular, elderly patients without pre-existing symptoms of gallbladder stones may be appropriate for endoscopic sphincterotomy, with conservative management of the gallbladder stones unless further symptoms arise. While most patients will have a straightforward management pathway (planned laparoscopic cholecystectomy with on-table cholangiogram and ERCP if necessary, or ERCP and sphincterotomy as definitive treatment if cholecystectomy is not undertaken), some centres may prefer to determine the presence of common bile duct stones by MRCP or EUS, before making the decision to undertake definitive treatment by either endoscopic sphincterotomy if stones are present, or laparoscopic cholecystectomy if the duct is clear. If there is no evidence of gallstone aetiology then early therapeutic endoscopy is not indicated. There is general agreement that in pancreatitis associated with cholangitis, early endoscopic sphincterotomy can bring about a marked improvement in the patients' condition and should be performed as soon as practicable, ideally within 24 h. In patients with severe acute pancreatitis without cholangitis there has been controversy over the benefit of early endoscopic therapy. Some recent evidence has clarified the indications for endoscopy, and it is now clear that if ERCP is attempted, sphincterotomy should always be performed to minimise the risk of procedure-induced cholangitis. In a patient with predicted mild acute pancreatitis there can be no benefit from prophylactic sphincterotomy as the risk of complications is low. Therefore, only patients with severe gallstone pancreatitis should be offered this intervention early [174].

A bile duct stone impacted at the duodenal papilla is an urgent condition that can rapidly lead to either suppurative cholangitis or acute pancreatitis due to almost complete obstruction of the bilio-pancreatic outflow. This study evaluated the clinical characteristics and results of endoscopic treatment for a bile duct stone impacted at the duodenal papilla. Forty-six patients who had been diagnosed with an impacted papillary stone were retrospectively reviewed. The typical features of acute cholangitis (Charcot's triad) and pancreatitis were

only observed only in 10 patients (22 %) and 17 patients (37 %), respectively. After the endoscopic retrograde cholangiopancreatography, 30 patients (65 %) were found to have a solitary stone impacting the duodenal papilla and 16 patients had one or more stones in the bile duct. On the radiological studies, the former patients were significantly associated more commonly with no visible stone or no bile duct dilatation. All impacted papillary stones were successfully removed by endoscopic sphincterotomy: 23 by a needle knife and 23 by a pull type papillotome. The procedure-related complications (n=7, 4 bleeding, 3 pancreatitis) were not serious and did not differ, based on endoscopic findings and the procedure used. Endoscopic sphincterotomy, either with a needle knife or a pull type papillotome, was safe and effective for removing the impacted papillary stone [175].

Gallstone pancreatitis is a consequence of ampullary obstruction by common bile duct (CBD) calculi. Magnetic resonance cholangiopancreatography (MRCP) has been advocated for routine use to diagnose choledocholithiasis. However, the selective use of MRCP in clinically equivocal situations has not been explored until now. One study examines the diagnostic value of selective MRCP in gallstone pancreatitis. It was conducted a retrospective audit of all presentations of gallstone pancreatitis between 2001 and 2007. Demographic data, clinical presentation, biochemical and radiological findings and outcomes were reviewed. There were 339 cases of gallstone pancreatitis during the study period; 236 patients were women and the mean age was 52 years. Overall, choledocholithiasis was diagnosed in 95 patients. A total of 117 patients underwent MRCP within a median of 4 days of admission, with 15 (14 %) showing choledocholithiasis. There was no significant difference in time to MRCP between positive and negative groups. Endoscopic retrograde cholangiopancreatography (ERCP)/intraoperative cholangiography (IOC) confirmed 13 of 15 stones within a median of 2.5 days. However, MRCP missed 8 cases of choledocholithiasis subsequently demonstrated on ERCP/IOC, where clinical suspicion remained after a negative MRCP. Its sensitivity was 62 percent and specificity 98 percent. The positive likelihood ratio was 6.5 and the negative likelihood ratio was 0.1. In all, 222 patients followed different clinical pathways with 82 CBD stones diagnosed by ERCP/IOC. It was concluded that selective MRCP is highly specific in gallstone pancreatitis but may not be sensitive enough to exclude choledocholithiasis in this context [176].

Early endoscopic spincterotomy

The effect of early endoscopic intervention (EI; within 72 hours) remains a controversial subject. This prospective study was aimed to evaluate the efficacy of early EI without fluoroscopy on severe acute biliary pancreatitis (SABP) in the intensive care unit (ICU). Fifty-three patients with SABP + ampullary obstruction in the ICU were divided randomly into 2 groups: conservative treatment in the ICU (CTI arm) and CTI + EI without the aid of fluoroscopy (CTI + EI arm). Decreased Acute Physiology and Chronic Health Evaluation II score was the major parameter to assess treatment efficacy. Endoscopic treatments including sphincterotomy + stone removal (17 cases) and nasobiliary drainage (4 cases) were successfully performed in all 21 enrolled patients without the aid of fluoroscopy in the ICU. Compared with CTI, CTI + EI significantly resulted in decreased (4 ± 2 vs 7 ± 2) Acute Physiology and Chronic Health Evaluation II score at day 10. No deaths were observed in the CTI + EI, whereas the CTI arm had 2 mortalities. It was concluded urgent endoscopic intervention without fluoroscopy is possible to be performed by endoscopists with the experience from high volume of procedures and is beneficial for the patients with severe acute biliary pancreatitis in the ICU or community hospital [177].

Based on the ampullary obstruction and reflux theory, six endoscopic retrograde cholangiopancreatography (ERCP) studies have investigated the effect of (early) biliary decompression versus conservative management on the course and outcome of patients with acute biliary pancreatitis (ABP) showing inconsistent and contradictory outcomes. It was investigated the opinion and attitude of Dutch gastroenterologists regarding the application of

(early) ERCP in the clinical management of ABP by means of a nationwide survey. An anonymous questionnaire was sent to all registered consultant gastroenterologists (n=283) across the Netherlands. The response rate was 52 percent. The vast majority of consulting gastroenterologists declared that early ERCP may be indicated in ABP (97 %). Fourteen percent stated that they always perform ERCP in ABP. The remainder of the respondents considered ERCP only if a concomitant condition is present such as a dilated CBD (95 %), co-existent cholangitis (87 %), common bile duct stone(s) (CBDS) (72 %), jaundice (59 %), ampullary stone (68 %) or (predicted) severe ABP (35 %). About half of the consultant gastroenterologists (52 %) considered the optimal time point for ERCP in ABP to be within 24 h after admission or symptom onset. If ERCP is performed for suspected APB, 55 percent of the respondents perform an endoscopic sphincterotomy (ES), regardless of the findings on cholangiography [178].

Cholecystectomy

It was explored whether admission volumes for cholecystectomy and pancreatitis were associated with receiving cholecystectomy after hospitalization for acute biliary pancreatitis. It was identified admissions for acute biliary pancreatitis in the Nationwide Inpatient Sample between 1998 and 2003. We used multivariate analysis to assess the association between likelihood of cholecystectomy and hospital volumes of cholecystectomy, pancreatitis, and endoscopic retrograde cholangiopancreatography (ERCP). The overall rate of cholecystectomy for biliary pancreatitis was 50 percent. After adjustment for confounders, the likelihood of cholecystectomy increased with every quartile of operation volume relative to the bottom quartile (adjusted odds ratios of 4.36, 7.92, and 12.51 for quartiles 2, 3, and 4, respectively). Pancreatitis volume was inversely correlated with likelihood of cholecystectomy (adjusted odds ratios of 0.72, 0.62, and 0.48 for quartiles 2, 3, and 4, respectively, versus bottom quartile). Admissions to hospitals in the top quartile for ERCP volume (>35 ERCPs per year) had 15 percent lower odds of cholecystectomy than the lowest quartile. Patients from rural areas and with lower income were disproportionately admitted to hospitals with lower cholecystectomy volumes. Centers with smaller cholecystectomy volumes are the least adherent to recommendations for cholecystectomy possibly because of hospital-level resource limitations [179].

Selective intraoperative cholangiography

Common bile duct (CBD) stones can cause serious morbidity or mortality, and evidence for them should be sought in all patients with symptomatic gallstones undergoing cholecystectomy. Routine intra-operative cholangiography (IOC) involves a large commitment of time and resources, so a policy of selective cholangiography was adopted. This study prospectively evaluated the policy of selective cholangiography for patients suspected of having choledocholithiasis, and aimed to identify the factors most likely to predict the presence of CBD stones positively. Data from 501 consecutive patients undergoing laparoscopic cholecystectomy (LC) for symptomatic gallstones, of whom 166 underwent IOC for suspected CBD stones, were prospectively collected. Suspicion of choledocholithiasis was based upon deranged liver function tests (past or present); history of jaundice (past or present) or acute pancreatitis; a dilated CBD or demonstration of CBD stones on imaging; or a combination of these factors. Patient demographics, intra-operative findings, complications and clinical outcomes were recorded. Sixty-four cholangiograms were positive (39 %). All indications for cholangiogram yielded positive results. Current jaundice yielded the highest positive predictive value (PPV; 86 %). A dilated CBD on pre-operative imaging gave a PPV of 45 percent for CBD calculi; a history of pancreatitis produced a 26 percent PPV for CBD calculi. Patients with the presence of several factors suggestive of CBD stones yielded higher numbers of positive cholangiograms. Of the 64 patients having a laparoscopic common bile duct exploration (LCBDE), four (6 %) required endoscopic

retrograde cholangiopancreatography (ERCP) for retained stones (94 % successful surgical clearance of the common bile duct) and one (2 %) for a bile leak. Of the 335 patients undergoing LC alone, three (1 %) re-presented with a retained stone, requiring intervention. There were 12 (7 %) requiring conversion to open operation. It was concluded that selective policy for intra-operative cholangiography yields acceptably high positive results. Pre-operatively, asymptomatic bile duct stones rarely present following LC; thus, routine imaging of the biliary tree for occult calculi can safely be avoided. Therefore, a rationing approach to the use of intra-operative imaging based on the pre-operative indicators presented in this paper, successfully identifies those patients with bile duct stones requiring exploration. Laparoscopic bile duct exploration, performed by an experienced laparoscopic surgeon, is a safe and effective method of clearing the bile duct of calculi, with minimal complications, avoiding the necessity for an additional intervention and prolonged hospital stay [180].

Intraductal ultrasonography (IDUS)

Intraductal ultrasonography (IDUS) is a useful procedure for diagnosing microlithiasis in the bile duct but it is not easy to differentiate between tiny echogenicity and real microlithiasis. We compared the echogenicity seen on IDUS and the findings of bile microscopy of bile that was collected in the common bile duct (CBD) to determine whether the echogenicity seen on IDUS is real microlithiasis. The prospective study involved a total of 30 patients who experienced biliary pain (n=11), acute cholecystitis (n=11) or indeterminate pancreatitis (n=8) without a filling defect or obstruction in the bile duct. IDUS was performed during endoscopic retrograde cholangiopancreatography (ERCP), followed by bile aspiration for bile microscopy. Endoscopic sphincterotomy (EST) was performed if definite echogenic materials were observed on IDUS. Of the 30 patients, 23 (77 %) had echogenic materials visible in the CBD on IDUS. Of these 23 patients, 13 (57 %) were found to have biliary crystals by microscopy. The size of the echogenic materials was the only significant factor associated with bile microscopy positivity. Using the receiver operating curve, the optimal size of the echogenicity to differentiate real microlithiasis was 1.4 mm. It was concluded that optimal concordance between IDUS and BM was observed when the size of the microlithiasis was greater than 1.4 mm; under these conditions the sensitivity and specificity were 71 percent and 75 percent, respectively. This information may be useful when deciding whether to perform endoscopic sphincterotomy [181].

ERCP during pregnancy

Biliary interventions during pregnancy are associated with risks to both the pregnancy and developing fetus. In one report it was summarized the experience with endoscopic interventions including endoscopic ultrasound (EUS) in the management of biliary disorders during pregnancy. Endoscopic retrograde cholangiopancreatographies (ERCPs) performed between 2003 through 2009 (n=607) were identified from a database, and cases of interventions during pregnancy were reviewed. All procedures were done using conscious sedation and lead shielding. Nine ERCPs (1.5 %) were performed in 8 pregnant patients. Their median gestational period was 22 weeks (range, 2-36 weeks). Two, 5 and 2 patients were in their first, second and third trimester, respectively. Indications for ERCP included obstructive jaundice (6 patients) cholangitis (2), and acute pancreatitis/obstructive jaundice (1). Two patients underwent EUS before ERCP. Fluoroscopy was used in 5 ERCPs (median 12 seconds; range 2-20 seconds), and the overall time for a ERCP ranged from 5 to 25 minutes. During ERCP endoscopic sphincterotomy was performed in 5 patients, stenting in 6, and balloon clearance in 3. One procedure caused complication in induction of labor. During pregnancy, there were 4 non-procedure related complications including acute cholecystitis (1), HELLP syndrome resulting in spontaneous abortion (1) and stent migrations (2). Five pregnancies had uncomplicated term deliveries, whereas 2 required urgent caesarian sections (one for fetal distress and 1 for cholangitis secondary to stent migration).

One patient was well in her second trimester during follow-up. Seven babies were well at birth with median APGAR scores of 9, and 10 at 5 and 10 minutes, respectively. One baby died of sudden death syndrome at age of 40 days. It was concluded that ERCP is a safe procedure for pregnant women. It can be conducted for biliary stenting and subsequent clearance after deliveries. EUS has a complementary role. Different strategies can be applied according to the conditions or expertise of endoscopists [182].

Experimentally

Obstructive jaundice causes multiple malfunctions in various organs, including the pancreas. It is not yet known, however, how this occurs. In the present study, it was experimentally induced obstructive jaundice through bile duct ligation (BDL) in rats. It was measured serum bilirubin, amylase and insulin levels and examined histological, immunohistochemical and cytological changes in the pancreas at 3 days, 1 week, and 4 weeks after the BDL. Morphometrical analysis was also conducted. Serum amylase levels steeply increased at 3 days and then decreased at 1 and 4 weeks after the BDL to lower than the control level. In contrast, the number of zymogen granules decreased at 3 days after the BDL, then increased and eventually surpassed the control group. On the other hand, serum insulin levels dramatically decreased at 3 days after the BDL, and then, at 1 week after the BDL, recovered to a level close to that of the control group. At 4 weeks after the BDL, however, the serum insulin levels again showed a marked decline. Slight decrease in insulin immunoreactivity and number of insulin granules were observed at 4 weeks after the BDL. Cholecystokinin receptors (CCK-R) were expressed in both acinar and islet cells; their immunoreactivity significantly decreased in the acinar cells at 4 weeks after the BDL. Our results suggest that CCK may play a role in regulating changes in the pancreas after obstructive jaundice [183].

Post-ERCP-pancreatitis

Bleeding is a feared complication of endoscopic sphincterotomy and papillectomy. Fibrin glue has been proposed as an effective adjunct in securing hemostasis. However, its use has been limited by the risk of early occlusion of the injecting needle, and its role has not been defined in the setting of refractory post-ERCP bleeding. It was presented a modified technique of endoscopic hemostasis with diluted fibrin glue in the setting of postsphincterotomy and postpapillectomy bleeds. In a case series in a tertiary-care academic medical center six patients with refractory post-ERCP bleeding were treated (3 after sphincterotomy and 3 after papillectomy) with fibrin glue injection. Successful endoscopic hemostasis with diluted fibrin glue injection was reached with one session of fibrin glue injection in all 6 patients. This case series provides indications that our modified injection technique of diluted fibrin glue allowed an easy submucosal injection and may be considered to be an effective endoscopic modality to treat refractory post-ERCP bleeding [184].

The objective of one study was to evaluate the efficacy of a pancreatic stent regarding the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis after aspiration of pure pancreatic juice in patients with intraductal papillary mucinous neoplasms. A retrospective study was made to assess the outcome in 121 consecutive patients with intraductal papillary mucinous neoplasms who underwent endoscopic aspiration of pure pancreatic juice for cytologic examination between 2001 and 2007. From 2001 to 2004, 58 patients did not undergo pancreatic stent insertion (the no-stent [nS] group). The remaining 63 patients did undergo stent insertion (stent [S] group). The overall incidence of post-ERCP pancreatitis was 11 (9 %). The incidences of post-ERCP pancreatitis in the S and nS groups were 8 (13 %) and 3 (5 %) which was a not significant difference, respectively. In the male patients and the patients with a smaller diameter of the main pancreatic ducts, post-

ERCP pancreatitis was seen more frequently in those in the S group (13 % and 21 %, respectively) than in those in the nS group (0 % and 0 %, respectively). It was concluded that a pancreatic stent did not seem to decrease the incidence of post-ERCP pancreatitis in patients with intraductal papillary mucinous neoplasms. Furthermore, the pancreatic stent seems to be potentially detrimental in male patients and in patients with small-diameter main pancreatic ducts [185].

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure widely used to diagnose and treat conditions of biliary or pancreatic ductal system. The post-ERCP severe acute pancreatitis (SAP) accompanied with duodenum perforation is rare but serious, remaining a challenge in clinic. In one report two such cases were described. Two Chinese women were treated for clinical suspicion of bile duct obstruction and underwent ERCP after admission. Both developed duodenum perforation and SAP after ERCP, and were managed in the intensive care unit (ICU) and required an organ-failure support. The surgical intervention of the peri-pancreatic debridement with lumbar-abdominal compound incisions and postoperative washing and drainage was performed, and the two patients recovered well. The therapeutic effect of the peri-pancreatic debridement with lumbar-abdominal compound incisions combined with postoperative washing and drainage in the patients of severe post-ERCP-pancreatitis (PEP) and duodenum perforation is satisfactory [186].

In a study of post-ERCP-pancreatitis mean serum trypsinogen concentrations were slightly below the upper reference limit (57 ng/mL) before ERCP examination, and then they were significantly increased thereafter. Before ERCP, there were no significant differences in the serum and urinary levels of the enzymes studied among the different final diagnoses. Serum and urine TAP levels and serum trypsinogen concentration showed no significant differences between patients who developed acute pancreatitis after ERCP and those who did not in any of the time intervals studied. The same behavior was present between patients who were treated prophylactically with gabexate and those who did not receive the drug. In this study, the percentage of postprocedural pancreatitis was higher than that reported in other studies coming from Italy, but only patients who underwent operative ERCP were enrolled, and acute pancreatitis had a mild course in all cases. In conclusion, TAP determination was of limited value in diagnosing post-ERCP acute pancreatitis [187].

Antibiotic prophylaxis in elective ERCP

The use of prophylactic antibiotics before endoscopic retrograde cholangiopancreatography (ERCP) is recommended by all major international gastroenterological societies, especially in the presence of an obstructed biliary system. Their use is intended to decrease or eliminate the incidence of complications following the procedure, namely cholangitis, cholecystitis, septicaemia, and pancreatitis. To assess the benefits and harms of antibiotics before elective ERCP in patients without evidence of acute or chronic cholecystitis, or acute or chronic cholangitis, or severe acute pancreatitis. It was searched The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and LILACS until March 2010. Relevant medical and surgical international conference proceedings were also searched. Only randomised clinical trials were included in the analyses, irrespective of blinding, language, or publication status. Participants were patients that underwent elective ERCP that were not on antibiotics, without evidence of acute or chronic cholecystitis, cholangitis, or severe acute pancreatitis before the procedure. It was compared patients that received prophylactic antibiotics before the procedure with patients that were given placebo or no intervention before the procedure. The review was conducted according to the recommendations of The Cochrane Collaboration as well as the Cochrane Hepato-Biliary Group. Nine randomised clinical trials (1573 patients) were included in the analyses. The majority of the trials had risks of bias. When all patients providing data for a

certain outcome were included, the fixed-effect meta-analyses significantly favoured the use of prophylactic antibiotics in preventing cholangitis (relative risk (RR) 0.54, 95 % confidence interval 0.33 to 0.91), septicaemia (RR 0.35, 95 % confidence interval 0.11 to 1.11), bacteraemia (RR 0.50, 95 % confidence interval 0.33 to 0.78), and pancreatitis (RR 0.54, 95 % confidence interval 0.29 to 1.00). In random-effects meta-analyses, only the effect on bacteraemia remained significant. Overall mortality was not reduced (RR 1.33, 95 % confidence interval 0.32 to 5.44). If one selects patients in whom the ERCP resolved the biliary obstruction at the first procedure, there seem to be no significant benefit in using prophylactic antibiotics to prevent cholangitis (RR 0.98, 95 % confidence interval 0.35 to 2.69, only three trials). It was concluded that prophylactic antibiotics reduce bacteraemia and seem to prevent cholangitis and septicaemia in patients undergoing elective ERCP. In the subgroup of patients with uncomplicated ERCP, the effect of antibiotics may be less evident. Further research is required to determine whether antibiotics can be given during or after an ERCP if it becomes apparent that biliary obstruction cannot be relieved during that procedure [188].

Prophylactic ulinastatin

Gallstone pancreatitis is a consequence of ampullary obstruction by common bile duct (CBD) calculi. Magnetic resonance cholangiopancreatography (MRCP) has been advocated for routine use to diagnose choledocholithiasis. However, the selective use of MRCP in clinically equivocal situations has not been explored until now. One study examines the diagnostic value of selective MRCP in gallstone pancreatitis. It was conducted a retrospective audit of all presentations of gallstone pancreatitis between 2001 and 2007. Demographic data, clinical presentation, biochemical and radiological findings and outcomes were reviewed. There were 339 cases of gallstone pancreatitis during the study period; 236 patients were women and the mean age was 52 years. Overall, choledocholithiasis was diagnosed in 95 patients. A total of 117 patients underwent MRCP within a median of 4 days of admission, with 15 (14 %) showing choledocholithiasis. There was no significant difference in time to MRCP between positive and negative groups. Endoscopic retrograde cholangiopancreatography (ERCP)/intraoperative cholangiography (IOC) confirmed 13 of 15 stones within a median of 2.5 days. However, MRCP missed 8 cases of choledocholithiasis subsequently demonstrated on ERCP/IOC, where clinical suspicion remained after a negative MRCP. Its sensitivity was 62 percent and specificity 98 percent. The positive likelihood ratio was 6.5 and the negative likelihood ratio was 0.1. In all, 222 patients followed different clinical pathways with 82 CBD stones diagnosed by ERCP/IOC. It was concluded that selective MRCP is highly specific in gallstone pancreatitis but may not be sensitive enough to exclude choledocholithiasis in this context [189].

Alcohol-induced acute pancreatitis

To study the association of binge drinking and the outcomes of severe acute pancreatitis a retrospective study included 347 patients with first-attack severe pancreatitis from 2001 to 2004 was performed. On the basis of the history of binge drinking or not, the patients were divided into the alcohol (n=77) and the control groups (n=270). Patient age and comorbidity were similar between the two groups. There were significantly more men (83 %) than women in the alcohol and the control groups (41 %). The two groups had significant differences in admission serum triglyceride levels (5.0 ± 5.0 vs 3.0 ± 3.5), Balthazar computed tomographic score (and Acute Physiology and Chronic Health Evaluation II score. Total mortality and the incidences of complications were higher in the alcohol group than in the control group [190].

In Goa, India

It was previously reported a high incidence of alcohol-related acute pancreatitis (AP) in Goa, India, where country-made alcoholic products are consumed in addition to the commercially available alcoholic products. It was aimed to analyze the composition of these country-made alcoholic products consumed by a population with a high incidence of alcohol-related AP. Three locally distilled alcoholic products (ethanol content, >20 %) regularly consumed by patients developing AP, as determined by responses in a patient questionnaire, were selected. Three commercially available products with comparable ethanol content (rum, whiskey, and brandy) were used for comparison. Representative samples were analyzed using gas chromatography/mass spectrometry. Compound assignments used mass spectral searches of the NIST library (2008). Commercially available rum, whiskey, and brandy used for comparison contained the 2 major constituents, ethanol and water. In addition, the country-made alcoholic products contained a higher level of by-products including long-chain alcohols (e.g. butanol, propanol), aldehydes (e.g. acetaldehyde), acids (e.g. acetic acid), and even traces of methanol. Conclusions: Country-made alcoholic products contain many compounds in addition to ethanol. Given the high incidence of alcohol-related AP in the population where these products are consumed, further evaluation of their constituents in relation to the induction of pancreatic damage is warranted [191].

Drug-induced acute pancreatitis

525 different drugs that can, as an adverse reaction, induce acute pancreatitis are listed in a WHO database. Compared to other causes drugs represent a relatively rare cause of pancreatitis. They should be considered as a triggering event in patients with no other identifiable cause of the disease, who takes medications that have been shown to induce pancreatitis. The prevalence of drug-induced pancreatitis is still unclear because most incidences have been documented only as isolated case reports. The overall incidence probably ranges from between 0.1 and 2 percent of pancreatitis cases. For only very few substances evidence from controlled trials has been obtained. Epidemiologic data suggest the risk of pancreatitis is highest for mesalazine (hazard ratio 3.5,) azathioprine (hazard ratio 2,5) and simvastatine (hazard ratio 1,8). Even when a definite association has been demonstrated it is often impossible to determine whether the drug, or the underlying condition for which the drug was taken has conferred the risk of pancreatitis (e.g. azathioprine and Crohns disease or pentamidine and HIV). Knowledge about the underlying pathophysiologic mechanisms as well as evidence for a direct causality often remains sparse. For only 31 drugs a definite causality has been established. The most frequently reported are mesalazine (nine cases in total, three cases with re-exposure), azathioprine (five cases in total, two cases with re-exposure) and simvastatin (one case in total, this one with re-exposure). As cause-effect relationship is generally accepted when symptoms re-occur upon re-challenge. Available data from case control studies suggest that even drugs with solid evidence for an association with pancreatitis only rarely cause the disease. Even when pancreatitis is induced as an adverse drug event the disease course is usually mild or even subclinical [192].

Incidence

Drug-induced acute pancreatitis is considered to be a rare diagnosis. The incidence of drug-induced acute pancreatitis is usually estimated from case reports. The aim of one study was to determine the incidence, etiology, and severity of drug-induced pancreatitis during a 2-year period in a tertiary hospital. The study was conducted as a retrospective analysis of all cases of pancreatitis in a university hospital (1,432 beds) in 2006-2007. All cases of acute pancreatitis were re-evaluated and divided according to the causative factor. In drug-induced

cases, the WHO Probability Scale for the evaluation of causality relationship was used. The inclusion criteria were met by 170 medical files. There were 91 (53 %) cases in men and 79 (47 %) in women, and mean age was 57 years old (5-91 years old). The etiology was in 53 percent biliary, 31 percent alcohol-induced, 12 percent other determined, and in 4 percent the cause could not be established. The proportion of drug-induced acute pancreatitis was 5 percent and it was the third most frequent cause of the AP. Azathioprine was the most frequent causative factor (three cases in two patients); all the other causative drugs were documented only in single cases: mesalazine, dexamethasone, ramipril, mycophenolate mofetil, cytarabine, and valproate. The diagnosis of drug-induced acute pancreatitis seems to be underestimated because of the difficulties in determining the causative agent and the need for a retrospective re-evaluation of the suspected causative factors. The disease is more probable in younger persons, women, and patients suffering from Crohn's disease [193].

Propofol

Drug-induced pancreatitis accounts for about 2 percent of acute pancreatitis. The aim of one study was to determine whether propofol and other medications are associated with increased risk for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. A retrospective study was conducted at a single tertiary care hospital. All patients who underwent ERCP from 2001 to 2004 were included. Diagnosis of acute post-ERCP pancreatitis was based on a consensus definition. A total of 506 patients underwent ERCP. The total incidence of post-ERCP pancreatitis was 7 percent. There was no significant difference in post-ERCP pancreatitis between patients who received propofol compared to patients who received midazolam and fentanyl (9 vs 6 %). Patients receiving an angiotensin receptor blocker were approximately 4 times more likely to develop post-ERCP pancreatitis (odds ratio 4.1; 95 % confidence interval 1.6 to 10.9). Patients younger than 65 years and smokers also had higher risk of developing acute post-ERCP pancreatitis than those who were older than 65 years (odds ratio 3.9; 95 % confidence interval 1.7 to 9.1) and non-smokers (odds ratio 2.8; 95 % confidence interval 1.3 to 6.2). It was concluded that propofol is a safe sedative drug for ERCP without additional risk of developing acute post-ERCP pancreatitis. Use of angiotensin receptor blockers, smoking and younger age are independent risk factors for post-ERCP pancreatitis [194].

Inhibition of 5-alpha-reductase

A 65-year-old male with a history of diabetes, hypertension, hyperlipidemia, gout, Barrett esophagitis, and chronic gastritis developed acute pancreatitis after taking one week of the herbal medicine, saw palmetto, for symptoms related to benign prostatic hyperplasia (BPH). Ultrasound and computed tomography ruled out cholelithiasis and obstruction, triglycerides were normal, and he had no recent infection or trauma. He had a history of occasional alcohol consumption, though there was no recent increased intake. The most likely cause of pancreatitis in this case was saw palmetto. Saw palmetto (*Serenoa repens*) is an herbal medication used primarily in the treatment of symptoms related to BPH. It has a high content of fatty acids and phytosterols which are thought to exert their effects by inhibiting the enzyme 5-alpha-reductase, thereby preventing the conversion of testosterone into dihydrotestosterone (DHT). It has been postulated that saw palmetto directly stimulates estrogenic receptors and inhibits progesterone receptors in the prostate tissue. A previous report implicated the estrogen/antiandrogen properties of saw palmetto as inducing hepatotoxicity in a patient. Additionally, it has also been postulated that stimulation of the estrogenic receptors may lead to increased triglyceride levels or induction of a hypercoagulable state that leads to pancreatic necrosis. Finally, inhibition of cyclooxygenase, a property of saw palmetto, may be linked to acute pancreatitis. Acute pancreatitis, a serious and sometimes fatal disorder may occur secondary to medications. Although the mechanism

is not fully known, this is the second case of acute pancreatitis that has been documented secondary to the herbal medication saw palmetto. It is important for clinicians to obtain detailed medication histories, including over-the-counter and herbal medications, in order to prevent further complications from occurring [195].

L-Asparaginase

L-asparaginase (L-ASNase) has been an essential component of multiagent chemotherapy for acute lymphoblastic leukemia in childhood for over three decades. There are currently two Food and Drug Administration (FDA)-approved formulations of L-ASNase derived from *Escherichia coli* and 1 non-FDA approved formulation derived from *Erwinia chrysanthemi*. Modifications in L-ASNase have included pegylation, which decreases drug immunogenicity and increases the half-life, allowing less frequent administration. Although L-ASNase is well-tolerated in most patients and causes little myelosuppression, significant toxicities occur in up to 30 percent of patients. Hypersensitivity is the most common toxicity of L-ASNase therapy and limits the further use of the drug. Other significant toxicities relate to a reduction in protein synthesis and include pancreatitis, thrombosis, central nervous system complications, and liver dysfunction [196].

Lisinopril and olanzapine

A case of acute pancreatitis associated with lisinopril and olanzapine is described. The additive effect of two known pancreatitis-causing medications resulted in increased risk and subsequent acute pancreatitis in this patient [197].

Orlistat

Orlistat is a pancreatic lipase inhibitor licensed for the treatment of obesity. As obesity rates increase and non-prescription dispensing of orlistat increases, an awareness of its adverse effects is of crucial importance as complications arise more frequently from increased use. Orlistat induced pancreatitis has been described only once previously, but without a diagnostic increase in serum amylase. It was reported the case of two patients who developed severe acute abdominal pain and elevated pancreatic enzymes at 2 and 10 days after starting orlistat. In one case no alternative precipitant was identified. In the other, a predisposing history of pancreatic injury was present. In both cases all other contributory causes were excluded. These reports suggest orlistat can trigger drug induced acute pancreatitis in certain patients. For patients presenting with abdominal pain soon after commencing orlistat, a diagnosis of pancreatitis must be considered [198].

Hypercalcemia-induced pancreatitis

Hypercalcemia is a rare but accepted cause for acute and chronic pancreatitis. Hypercalcemia-related pancreatitis is mainly secondary to primary hyperparathyroidism (pHPT). Few case reports showed association of familial hypocalciuric hypercalcemia (FHH) and pancreatitis. We report the case of a patient with acute pancreatitis attributed to the association of FHH (with calcium-sensing receptor – CaSR – gene mutation) and SPINK1 gene mutation. A 37-year-old white male was admitted for acute pancreatitis in February 2007. His medical history included four recurrent acute pancreatitis and cholecystectomy after the first acute pancreatitis in 1992. His family history was noncontributory. His alcohol consumption was 50 grams a week for a year. The laboratory tests were unremarkable. An abdominal computed tomographic scan showed no chronic pancreatitis (neither calcification nor duct abnormalities) but peripancreatic inflammation only. Results of magnetic resonance cholangiopancreatography and endoscopic ultrasound were normal. Hypercalcemia with

nonadapted parathormone level was explored: result of parathyroid ultrasonography was normal. Heterozygous missense mutation (p.Pro682Leu in exon 7) in the CaSR was identified by direct DNA sequencing. Furthermore, analysis in genes involved in the different forms of hereditary pancreatitis was performed because of the young age of the patient. A heterozygous IVS3+2T>C mutation was found in the SPINK1 gene coding for the inhibitor of the cationic trypsinogen. No mutation in the gene coding for the cationic trypsinogen (PRSS1) and none of the CFTR gene were found. Outpatient follow-up showed a subnormal serum calcium concentration varying between 2.55 and 2.66 mmol/L, and there was no further pancreatitis without any hypocalcemic treatment. Hypercalcemia is known to be associated with acute and chronic pancreatitis. It was reported a rare case of acute pancreatitis caused by the association of a SPINK1 gene heterozygous mutation and FHH due to a mutation of the CaSR. This heterozygous missense mutation (p.Pro682Leu in exon 7) was never described before. The most common cause for hypercalcemia-related pancreatitis is pHPT. The relationship between pHPT and acute pancreatitis is controversial, and the prevalence of pancreatitis in pHPT patients varies widely, from 1.5 percent (that did not significantly differ from the frequency of acute pancreatitis reported in the normal population) to 6.8 percent. Physiopathologic causes of hypercalcemia-related pancreatitis remain unknown, but autodigestion of the pancreatic parenchyma induced by premature activation of trypsinogen could be involved. No threshold of calcemia is clearly identified as the triggering factor for pancreatitis, but in the reports of hypercalcemia-related pancreatitis, calcemia varied between 2.7 and 3.2 mmol/L. Familial hypocalciuric hypercalcemia is a hereditary autosomal dominant disorder, usually asymptomatic, due to inactivating mutation of the CaSR, mapped to the long arm of chromosome. It should be considered in the differential diagnosis of hypercalcemia, without inhibition of PTH secretion, particularly when the urinary calcium excretion is low. The CaSR is expressed in tissues involved in calcium homeostasis, including kidney, parathyroid glands, and bone cells. The CaSR is also identified in human pancreatic ducts and acinar cells, but its role in the pathogenesis of pancreatitis remains unclear. A heterozygous inactivating CaSR mutation leads to FHH, but homozygous mutations result in severe neonatal pHPT. In contrast to pHPT, there are very few reports of FHH and pancreatitis. Differential diagnosis between pHPT and FHH is of clinical relevance because parathyroidectomy usually fails to correct the hypercalcemia in FHH [199].

Hypertriglyceridemia induced acute pancreatitis

Severe hypertriglyceridemia is a known cause of acute pancreatitis, and apheresis treatment, most commonly plasmapheresis, has been used to treat patients with drug refractory hypertriglyceridemia for more than 30 years. It was reported a case in which a woman with Crohn's disease and type 2 diabetes mellitus developed recurrent episodes of acute pancreatitis due to extreme hypertriglyceridemia. After the initiation of lipoprotein apheresis from whole blood, a marked reduction of triglyceride and lipoprotein levels was observed. Some inflammatory parameters were increased even if most of the cytokines were not detectable, indicating good biocompatibility of the filter. It was concluded that triglyceride levels were lowered after initiating selective lipoprotein apheresis. More importantly, the patient did not experience any relapses of pancreatitis after the treatment was started. Hence this treatment is feasible in drug refractory hypertiglyceridemia, but the treatment concept needs to be tested in additional studies [200].

Chylomicronaemia syndrome is a rare disorder primarily caused by a genetic defect which increases triglycerides, combined with a secondary inducing factor. It was describe the fatal course of a 33-year-old, pregnant woman with known dyslipidaemia who had been treated with in vitro fertilisation and developed chylomicronaemia syndrome with severe

hypertriglyceridaemia, hypertriglyceridaemia-induced acute pancreatitis and septic shock [201].

Nicotine gum-induced pancreatitis

It was reported a case of acute pancreatitis in an otherwise healthy 57-year-old man who attributed his condition to Nicorette gum. A 57-year-old white man, attended the emergency department with severe epigastric pain, nausea and vomiting, and a raised serum amylase level of 800 Kg/L. His condition was diagnosed as acute pancreatitis, and he revealed that he had experienced a similar bout two years previously, also necessitating admission to hospital. He was commenced on intravenous fluids and kept nil by mouth. Twenty-four hours after admission, he was scored using the Modified Glasgow Score > 3 (raised leukocytes, lactate dehydrogenase, and serum glucose levels). His symptoms resolved quickly, and an abdominal ultrasound scan revealed an unremarkable biliary tree with no gallstones. He drank minimal amounts of alcohol at approximately 7 units per week, and his F-glutamyl transferase level was normal (24 IU/L). He had not been involved in any trauma to his abdomen and was not taking any regular medications or over-the-counter analgesia. His serum calcium, glucose, and triglyceride levels were all within reference range. He had no significant medical history other than mild chronic obstructive pulmonary disease for which he used as required salbutamol but no inhaled steroids. The patient reported that 1 week before this and his previous admission with acute pancreatitis, he had begun to use nicotine gum in an effort to quit smoking. He used roughly 10 pieces of 4-mg nicotine gum per day for 7 days (40 mg of nicotine per day) with no cigarettes and, on both occasions, developed acute epigastric pain with nausea and vomiting requiring admission, and upon admission, his condition was diagnosed as acute pancreatitis. On each admission, his symptoms have resolved with cessation of the gum and simple conservative measures. The mechanism by which nicotine induces such effects is perhaps mediated via signal transduction pathways in the pancreatic acinar cell, leading to enhanced levels of intracellular calcium release, resulting in cytotoxicity and eventual cell death [202].

Ischemia induced acute pancreatitis

Ischemia is an established cause of acute pancreatitis; however, acute pancreatitis has never been reported after cardiac arrest. It was therefore reported a case of acute pancreatitis following cardiac arrest with prolonged cardiopulmonary resuscitation in a 58-year-old man, the mechanism of which is likely to be ischemic. The patient developed severe ischemic encephalopathy, leading to death. Possible causes of acute pancreatitis in a context of cardiopulmonary resuscitation are discussed. In case of abdominal distension following cardiac arrest, diagnoses of mesenteric ischemia and acute ischemic pancreatitis should be considered. Such digestive complications occurring after cardiac arrest probably reflect the severity of the ischemia [203].

It was reported the case of a 72-year-old lady who presented with acute pancreatitis. Seven days later, she experienced an acute episode of chest pain associated with the pronounced electrocardiographic changes and elevated cardiac enzymes. Although subsequent coronary angiography was normal, a left ventriculogram demonstrated a marked area of apical akinesia and hyperkinesia of the basal left ventricular walls. It was believed to be the first case of pancreatitis induced takotsubo cardiomyopathy in the international literature [204].

Association with inflammatory bowel disease

Crohn's disease and ulcerative colitis, together popularly known as inflammatory bowel disease (IBD), are characterized by a number of extraintestinal manifestations. Although infrequent, acute pancreatitis, and less often chronic pancreatitis, may occur as a result of the disease itself or secondary to the medications used in the treatment. The increased incidence of acute pancreatitis in Crohn's disease can be explained based on the high predisposition to cholesterol as well as pigment stones as a result of ileal disease, anatomic abnormalities of the duodenum, immunologic disturbances associated with IBD, and, above all, to the side effects of many medications used in the treatment. Sulfasalazine, 5-aminosalicylic acid, azathioprine, and 6-mercaptopurine are well known to cause acute pancreatitis as a result of a possible idiosyncratic mechanism. Crohn's disease and ulcerative colitis share many clinical manifestations and treatment modalities. Nonspecific elevations of serum pancreatic enzymes in IBD make it difficult to avoid over diagnosis of acute pancreatitis, particularly in patients with Crohn's disease who suffer from abdominal pain often. The IBD-pancreas association is further reflected in many reports of exocrine as well as endocrine pancreatic insufficiency [205].

Burkitt lymphoma presenting as acute pancreatitis

Acute pancreatitis is a rare initial presentation of non-Hodgkin lymphoma with few reported cases described in older adults and even fewer in children. MRI features of Burkitt lymphoma of the pancreas are sparse in the radiologic literature. It was presented a 6-year-old boy who presented with pancreatitis and obstructive jaundice, which was the result of Burkitt lymphoma of the pancreas. The imaging findings of pancreatic involvement of Burkitt lymphoma on MRI were discussed and the contributory role of the radiologist in guiding the appropriate clinical work-up of this disease is highlighted [206].

In juvenile SLE

Acute pancreatitis (AP) is a rare but life-threatening manifestation of juvenile systemic lupus erythematosus (JSLE). The objective of one study was to evaluate the prevalence and clinical features of AP in a JSLE population. AP was defined according to the presence of abdominal pain or vomiting associated to an increase of pancreatic enzymes and/or pancreatic radiological abnormalities. Of note, in the last 26 years, 5367 patients were followed up at our Pediatric Rheumatology Unit and 263 (5 %) of them had JSLE diagnosis (ACR criteria). AP was observed in 4 percent (11/263) of JSLE patients. The median of age of the JSLE patients at AP diagnosis was 12 years (9-18). All of them had lupus disease activity at AP onset. Three patients were receiving corticosteroids before AP diagnosis. Interestingly, 10/11 JSLE patients fulfilled preliminary guidelines for macrophage activation syndrome, three of them with macrophage hemophagocytosis in bone marrow aspirate and hyperferritinemia. The hallmark of this syndrome is excessive activation and proliferation of T lymphocytes and macrophages with massive hypersecretion of proinflammatory cytokines and clinically it is characterized by the occurrence of unexplained fever, cytopenia and hyperferritinemia. AP treatment was mainly based on intravenous methylprednisolone. Four JSLE patients with AP died and two developed diabetes mellitus. In conclusion, acute pancreatitis was a rare and severe manifestation in active pediatric lupus. The association between pancreatitis and macrophage activation syndrome suggests that the pancreas could be a target organ of this syndrome and that pancreatic enzyme evaluation should also be carried out in all patients [207].

Non-surgical treatment

The aim of one study was to investigate the therapeutic effects and the mechanism of combination of hemofiltration and peritoneal dialysis in the treatment of severe acute pancreatitis. Fifty-one cases of severe pancreatitis were randomly divided into the hemofiltration and peritoneal dialysis group (treated group, 36 patients) and a control group, (15 patients). Both groups were treated by the same traditional methods. The relief time of abdominal pain and abdominal distension, computed tomographic scores, acute physiology and chronic health enquiry II scores, length of stay, cost of hospitalization, operability, and recovery rate of the 2 groups were compared. The concentration of tumor necrosis factor-[alpha], IL-6, and IL-8 in serum and ascites volumes was determined before and after treatment. The mean time of abdominal pain relief, amelioration of abdominal distension, decrease of computed tomographic scores, acute physiology and chronic health enquiry II scores, the mean length of stay, and cost of hospitalization of the treated group were significantly shorter or less than those of the control group. The aforementioned inflammatory cytokines, detected at the end of 1 day and 2 days after treatment, were decreased significantly compared with those observed in pretherapy and the control group [208].

Fluid treatment

It was evaluated the impact of the initial intravenous fluid resuscitation rate within the first 24 h of presentation to the emergency room on important outcomes in severe acute pancreatitis. Patients presenting directly with a diagnosis of severe acute pancreatitis were identified retrospectively. Patients were divided into two groups – those who received >33 percent (“early resuscitation”) and <33 percent (“late resuscitation”) of their cumulative 72-hour intravenous fluid volume within the first 24 h of presentation. The primary clinical outcomes were in-hospital mortality, development of persistent organ failure, and duration of hospitalization. Seventeen patients were identified in the “early resuscitation” group and 28 in the “late resuscitation” group and there were no baseline differences in clinical characteristics between groups. Patients in the “late resuscitation” group experienced significantly greater mortality than those in the “early resuscitation” group (18 vs 0 %) and demonstrated a trend toward greater rates of persistent organ failure (43 vs 35 %). There was no difference in the total amount of fluid given during the first 72 h. Thus, patients with severe acute pancreatitis who do not receive at least one third of their initial 72-hour cumulative intravenous fluid volume during the first 24 h are at risk for greater mortality than those who are initially resuscitated more aggressively [209].

Prediction of response to fluid treatment

Rapid fluid loading is standard treatment for hypovolemia. Because volume expansion does not always improve hemodynamic status, predictive parameters of fluid responsiveness are needed. Passive leg raising is a reversible maneuver that mimics rapid volume expansion. Passive leg raising-induced changes in stroke volume and its surrogates are reliable predictive indices of volume expansion responsiveness for mechanically ventilated patients. We hypothesized that the hemodynamic response to passive leg raising indicates fluid responsiveness in nonintubated patients without mechanical ventilation. It was investigated consecutive nonintubated patients, without mechanical ventilation, considered for volume expansion. It was assessed hemodynamic status at baseline, after passive leg raising, and after volume expansion (500 mL 6 % hydroxyethyl starch infusion over 30 mins). Among 34 patients included in this study, 14 had a stroke volume increase of ≥ 15 percent after volume expansion (responders). All patients included in the study had severe sepsis (n=28; 82%) or acute pancreatitis (n=6; 18 %). The Deltastroke volume ≥ 10 percent predicted fluid responsiveness with sensitivity of 86 percent and specificity of 90 percent. The Deltapulse pressure ≥ 9 percent predicted fluid responsiveness with sensitivity of 79 percent and

specificity of 85 percent. The deltavelocity of femoral artery flow ≥ 8 percent predicted fluid responsiveness with sensitivity of 86 percent and specificity of 80 percent. It was concluded that changes in stroke volume, radial pulse pressure, and peak velocity of femoral artery flow induced by passive leg raising are accurate and interchangeable indices for predicting fluid responsiveness in nonintubated patients with severe sepsis or acute pancreatitis [210].

Regional infusion of protease inhibitors

A randomized controlled trial was conducted to clarify whether continuous regional arterial infusion (CRAI) of protease inhibitor and antibiotic could reduce mortality rate of severe acute pancreatitis (SAP). Seventy-eight patients with SAP were included in the study. Thirty-nine patients were treated with CRAI, 31 patients completed the study; and another group of 39 patients was treated without CRAI therapy. Groups were well matched in clinical characteristics. The CRAI patients were treated continuously with nafamostat mesylate 240 mg/d and imipenem 1 g/d for 5 days via one of the arteries perfusing the pancreas. Later, imipenem was given intravenously (0.5 g every 8 hours) for 9 days. The non-CRAI patients received imipenem (0.5 g every 8 hours) intravenously for 14 days. Statistical analysis of the intention-to-treat (ITT) group was performed. Lack of septic complications was observed in 23 patients with CRAI therapy and 20 non-CRAI patients (not significant). The additional antibiotics were applied in 8 of CRAI patients and in 18 non-CRAI. Mortality rate was 5.1 percent in CRAI and 23.1 percent in non-CRAI group. Urgent surgical intervention was necessary in 10 percent of CRAI patients and in 33 percent of non-CRAI, which was a significant difference. The results show that CRAI of protease inhibitor and antibiotic is effective in preventing complications and in reducing mortality rate in severe acute pancreatitis (also outside Japan) [211].

Continuous high-volume hemofiltration

To evaluate the efficacy of adjunctive continuous high-volume hemofiltration (HVHF) in patients with severe acute pancreatitis 75 patients admitted to the intensive care unit for severe acute pancreatitis from 2006 to 2009 were followed prospectively. Patients were divided into 4 groups according to whether they accepted continuous HVHF (42 vs 33) and if they showed signs of acute kidney injury. Patients of the 4 groups were comparable at baseline. The 28-day survival rate was significantly higher in patients who accepted HVHF (81 % vs 58 %), especially in those without acute kidney injury (95 % vs 67 %). Furthermore, after 72 hours of therapy, the patients who accepted HVHF had significantly better Acute Physiology and Chronic Health Evaluation II scores (17 ± 4 vs 13 ± 3), body temperature, urine volume, and base excess. However, the improvement in patients who did not accept HVHF was not so obviously. It was concluded that high-volume hemofiltration was associated with improved clinical outcome in acute pancreatitis patients, and should be initiated before kidney injury appearance [212].

Immunological aspects

The aim of one study was to observe the dynamic changes of immunity for patients with severe acute pancreatitis (SAP) and intervention by traditional Chinese medicine. Twenty-three patients who met the inclusion criteria were randomized to combined treatment of traditional Chinese medicine and Western medicine (TCM) or conventional western medicine treatment (WM) groups. The clinical data for all patients were collected. Peripheral venous blood samples were obtained from patients on days 1, 7, 14, and 28 after admission. Biochemical data including the percentage of CD4+/CD8+/natural killer (NK) cells/B lymphocytes/HLA-DR and CD4+/CD8+ ratio in serum were determined by flow cytometer. Patients' characteristics and immunity at admission were similar between the two groups.

The secondary infection was different. The levels of T-lymphocyte subsets in the TCM group were quite different from the WM group, with much more the percentage of CD4+ and the CD4+/CD8+ ratio on days 7, 14, and 28 and much less the percentage of CD8+ on days 14 and 28. On days 14 and 28, the levels of NK cells and B lymphocytes were significantly higher in the TCM group compared with the controls. Compared with the TCM group, the levels of HLA-DR were significantly decreased in the WM group on days 7, 14, and 28. The immune dysregulation exists in the development and progression of SAP. The combined treatment of traditional Chinese medicine and western medicine can upregulate the patient's immune and maintain the immune balance [213].

Angiotensin II receptor blockers

A protective effect by angiotensin II receptor blockers (ARB) on acute pancreatitis has been suggested experimentally, but clinical evidence is scarce. It was conducted a population-based case-control study using The Health Improvement Network in the United Kingdom, comprising about 167,000 hypertensive patients in the study period 1996-2005. In multivariate logistic regression analysis, odds ratios were calculated with 95 percent confidence intervals (CI). Adjustments included sex, age, calendar year, body mass index, tobacco smoking, alcohol, general practitioner visits per year, and various antihypertensive medications with regard to exposure to ARB, and risk of acute pancreatitis. Among 633,281 person-years at risk, 265 new cases of acute pancreatitis were identified. Current users of ARB had a 37 percent statistically non-significant reduced risk of developing acute pancreatitis as compared to non-users (odds ratio 0.63; 95% confidence interval 0.38 to 1.02). No clear association was found between use of other antihypertensive drugs and risk of acute pancreatitis, but the study adds some support to previous experimental findings. Use of ARB might be associated with a reduced risk of acute pancreatitis [214].

Prophylactic antibiotics

In an update of Cochrane Database Syst Rev 2006 it was determine the efficacy and safety of prophylactic antibiotics in acute pancreatitis complicated by CT proven pancreatic necrosis. Searches were updated in November 2008 in The Cochrane Library (Issue 2, 2008), MEDLINE, EMBASE, and CINAHL. Conference proceedings and references from found articles were also searched. It was searched for randomised controlled trials (RCTs) comparing antibiotics versus placebo in acute pancreatitis with CT proven necrosis. Primary outcomes were mortality and pancreatic infection rates. Secondary end-points included non pancreatic infection, all sites infection, operative rates, fungal infections, and antibiotic resistance. Subgroup analyses were performed for antibiotic regimen (beta-lactam, quinolone, and imipenem). Seven evaluable studies randomised 404 patients. There was no statistically significant effect on reduction of mortality with therapy: 8 percent versus controls 14 percent, and infected pancreatic necrosis rates: 20 percent versus controls 24 percent. Non-pancreatic infection rates and the incidence of overall infections were not significantly reduced with antibiotics: 24 percent versus 36 percent; 38 percent versus 52 percent respectively. Operative treatment and fungal infections were not significantly different. Insufficient data were provided concerning antibiotic resistance. With beta-lactam antibiotic prophylaxis there was less mortality (9 % treatment, 15 % controls), and less infected pancreatic necrosis (17 % treatment group, 24 % controls) but this was not statistically significant. The incidence of non-pancreatic infections was non-significantly different (21 % vs 33 %), as was the incidence of overall infections (34 % vs 53 %), and operative treatment rates. No significant differences were seen with quinolone plus imidazole in any of the end points measured. Imipenem on its own showed no difference in the incidence of mortality, but there was a significant reduction in the rate of pancreatic infection (relative risk 0.34, 95

% confidence interval 0.13 to 0.84). The authors concluded that there was no benefit of antibiotics in preventing infection of pancreatic necrosis or mortality was found, except for when imipenem (a beta-lactam) was considered on its own, where a significantly decrease in pancreatic infection was found. None of the studies included in this review were adequately powered. Further better designed studies are needed if the use of antibiotic prophylaxis is to be recommended [215].

Peripancreatic necrosis

Peripancreatic necrosis determines clinical severity in acute pancreatitis. Early markers predicting peripancreatic necrosis and clinical severity are lacking. Because adipocytes of peripancreatic adipose tissue secrete highly active adipocytokines, the aim of one study was to investigate whether adipocytokines are able to serve as early markers predicting peripancreatic necrosis and clinical severity. A total of 50 patients (20 women, 30 men) with acute pancreatitis were included in this noninterventional, prospective, and monocentric cohort study on diagnostic accuracy. Clinical severity was classified by the Ranson score and the APACHE (Acute Physiology And Chronic Health Evaluation) II score. Pancreatic and peripancreatic necrosis were quantified by using the computed tomography-based Balthazar score, the Schroeder score, and the pancreatic necrosis score. Adiponectin, leptin, and resistin were measured at admission and daily for at least 10 days by enzyme-linked immunosorbent assay. In contrast to admission C-reactive protein values, admission resistin values were significantly correlated with clinical severity and even with clinical end points such as death and need for interventions. Admission resistin levels were significantly elevated in patients with higher pancreatic and extrapancreatic necrosis scores. It was shown by receiver-operator characteristics that admission resistin concentration provides a positive predictive value of 89 percent in predicting the extent of peripancreatic necrosis (sensitivity, 80 %; specificity, 70 %) by using a cutoff value of 11.9 ng/mL. It was concluded that admission resistin concentration serves as an early predictive marker of peripancreatic necrosis and clinical severity in acute pancreatitis. Resistin may have potential for clinical use as a new and diagnostic serum marker [216].

Peripancreatic fluid collection in acute pancreatitis

To evaluate the ability of contrast-enhanced computerized tomography (CECT) to characterize the nature of peripancreatic collections 25 patients with peripancreatic collections on CECT and who underwent operative intervention for severe acute pancreatitis were retrospectively studied. The collections were classified into (1) necrosis without frank pus; (2) necrosis with pus; and (3) fluid without necrosis. A blinded radiologist assessed the preoperative CTs of each patient for necrosis and peripancreatic fluid collections. Peripancreatic collections were described in terms of volume, location, number, heterogeneity, fluid attenuation, wall perceptibility, wall enhancement, presence of extraluminal gas, and vascular compromise. Fifty-four collections were identified at operation, of which 45 (83 %) were identified on CECT. Of these, 25/26 (96 %) had necrosis without pus, 16/19 (84 %) had necrosis with pus, and 4/9 (44 %) had fluid without necrosis. Among the study characteristics, fluid heterogeneity was seen in a significantly greater proportion of collections in the group with necrosis and pus, compared to the other two groups (94 % vs 48 % and 25 %). Among the wall characteristics, irregularity was seen in a greater proportion of collections in the groups with necrosis with and without pus, when compared to the group with fluid without necrosis (88 % and 71 % vs 25 %). The combination of heterogeneity and presence of extraluminal gas had a specificity and positive likelihood ratio of 92 percent and 5.9, respectively, in detecting pus. It was concluded that most of the peripancreatic collections seen on CECT in patients with severe acute pancreatitis who

require operative intervention contain necrotic tissue. CECT has a somewhat limited role in differentiating the different types of collections [217].

Necrosis

There is no consistency between the individual studies in the literature on whether organ failure (OF) or infected pancreatic necrosis (IPN) is the main determinant of severity in acute pancreatitis. It was aimed to statistically aggregate the available data and determine the pooled influence of OF and IPN on mortality in patients with acute pancreatitis. The search for relevant observational studies was undertaken in the MEDLINE, EMBASE, and Scopus electronic databases, as well as in the proceedings of major gastroenterology meetings. The summary estimates are presented as relative risk (RR) and 95 percent confidence interval. Fourteen studies comprising 1478 patients with acute pancreatitis were meta-analyzed. A total of 600 patients developed OF and 179 of them died (mortality, 30 %); 314 patients developed IPN and 102 of them died (mortality, 32 %). In a stratified analysis, patients with OF and IPN had a significantly higher risk of death in comparison with patients with OF and no IPN (RR 1.94; 95 % confidence interval 1.32 to 2.85) and in comparison with patients with IPN and no OF (RR 2.65; 95 % confidence interval 1.30 to 5.40). It was concluded that in patients with acute pancreatitis, the absolute influence of OF and IPN on mortality is comparable and thus the presence of either indicates severe disease. The relative risk of mortality doubles when OF and IPN are both present and indicates extremely severe disease or critical acute pancreatitis [218].

Walled-off necrosis

Walled-off pancreatic necrosis (WOPN), formerly known as pancreatic abscess is a late complication of acute pancreatitis. It can be lethal, even though it is rare. One critical review provided an overview of the continually expanding knowledge about WOPN, by review of current data from references identified in Medline and PubMed, to September 2009, using key words, such as WOPN, infected pseudocyst, severe pancreatitis, pancreatic abscess, acute necrotizing pancreatitis (ANP), pancreas, inflammation and alcoholism. WOPN comprises a later and local complication of ANP, occurring more than 4 weeks after the initial attack, usually following development of pseudocysts and other pancreatic fluid collections. The mortality rate associated with WOPN is generally less than that of infected pancreatic necrosis. Surgical intervention had been the mainstay of treatment for infected peripancreatic fluid collection and abscesses for decades. Increasingly, percutaneous catheter drainage and endoscopic retrograde cholangiopancreatography have been used, and encouraging results have recently been reported in the medical literature, rendering these techniques invaluable in the treatment of WOPN. Applying the recommended therapeutic strategy, which comprises early treatment with antibiotics combined with restricted surgical intervention, fewer patients with ANP undergo surgery and interventions are ideally performed later in the course of the disease, when necrosis has become well demarcated [219].

Open necrosectomy

It was examined the clinical outcome in a consecutive cohort of patients undergoing open necrosectomy for postinflammatory necrosis. The report provides data on outcome from open necrosectomy in a tertiary referral Hepatobiliary unit over the last decade. During the period 2000 to 2008, 1535 patients were admitted with a final discharge code of acute pancreatitis. Twenty-eight (1.8 %) of all admissions underwent open surgical necrosectomy. Twenty-four (86 %) were tertiary referral patients. The median APACHE II score on admission was 11 (5-26). Median logistic organ dysfunction score on admission was 3 (0-10). Median LODS score after surgery was 2 (0-8). Twenty patients (71 %) underwent

radiologically guided drainage of collections before surgery. Thirty-day mortality occurred in 2 (7 %), 4 further deaths occurred in patients after discharge from intensive care resulting in a total of 6 (22 %) episode-related deaths. Modern open necrosectomy can be performed without the procedure-related deterioration in organ dysfunction associated with major debridement. Multidisciplinary care with an emphasis on aggressive radiologic intervention before and after surgery results in acceptable outcomes in this cohort of critically ill patients. Newer laparoscopic techniques must demonstrate similar outcomes in the setting of stage-matched severity before wider acceptance [220].

Endoscopic approach

Management of infected pancreatic necrosis with necrosectomy is challenging, and the mainstay is open surgical necrosectomy. However, the surgical procedure is associated with high morbidity (13-54 %) and mortality (6-25 %). Percutaneous drainage is effective for a subgroup of patients but not effective when thick purulent and necrotic materials are present within the cavity. In recent years, endoscopic treatments with transgastric endoscopic necrosectomy were introduced as an effective alternative management. It was reported a case of extensive infected pancreatic necrosis involving the head, body, and tail, unsuitable for surgery, in a patient treated with transgastric plus transduodenal approaches. A 50-year-old man with a recent episode of acute pancreatitis from biliary stones was transferred for high-grade fever and diagnosis upon computed tomographic scan of a large pancreatic collection. Upon admission, the patient had a fever with a temperature of 40°C. The CT scan highlighted a large collection (about 17 cm) in the head, body, and tail with multiple air bubbles, suggestive of infected pancreatic necrosis; thrombosis of the portal, superior mesenteric, and splenic veins with perisplenic, perigastric, and mesenteric collateral vessels; and splenomegaly. Antibiotics were started. Because of the diffuse vascular thrombosis with large collateral vessels network, the patient was not considered a candidate for surgery. Endoscopic ultrasound (EUS) to create a fistula between the stomach or the duodenum and a large pancreatic collection was selected as the best approach for this situation. An EUS-guided fine-needle aspiration through the posterior gastric wall revealed purulent and necrotic materials. Contrast injection revealed the large collection, a guide wire was placed, and the needle was removed. A progressive pneumatic dilatation was performed from 4 to 12 mm, and two 10F double pigtail stents were placed, highlighting abundant solid and purulent materials. The procedure was completed a week later with dilatation at 18 mm and necrosectomy, inserting the gastroscope in the pancreatic area and removing debris and pus with Dormia and biopsy forceps. At the end of the procedure, a metal stent was placed, and irrigation was performed with a large amount of saline (1500 mL). Despite a prompt improvement of the general conditions, after 1 week, the patient developed a high-grade fever and the CT scan showed a persistence of the necrosis in the region of the pancreatic head. It was then performed the same procedure of necrotic tissue debridement from the duodenal bulb as follows: EUS puncture, fistula creation, dilation at 18 mm, and necrosectomy with temporary metal stent placement for irrigation. The patient's condition improved significantly. He showed no procedural complications. An upper endoscopy was performed 15 days later, and the transgastric and transduodenal stents were removed with a snare without problems. A follow-up CT scan at 1 week, 3 months, and 1 year showed a complete resolution of the infected necrosis. In conclusion, the size of the necrotic collection rendered transgastric necrosectomy alone to be ineffective. The combined approach via gastric and duodenal-pancreatic fistula creation was effective and feasible, and the patient showed prompt recovery with no problem. These results were still maintained after 1 year with no relapse [221].

A 73-year-old male developed fever and jaundice 6 months after an episode of acute necrotizing pancreatitis. During endoscopic retrograde cholangiography, a distal bile duct compression was documented and stent insertion led to resolution of jaundice, however, the febrile condition persisted. A pancreatic necrosis measuring 11x7 cm was shown by

computed tomography and the patient was referred for necrosectomy. During the first endoscopic session, spontaneous drainage of pus was observed in the duodenal bulb. Therefore, the pancreatic necrosis was first punctured under endoscopic ultrasound-guidance transduodenally. The pancreatic necrosis was then additionally punctured transgastrically and the necrotic cavity was entered with a standard upper gastrointestinal scope. Despite extensive irrigation and necrosectomy we felt the transgastric approach was not sufficient enough to treat the large necrotic cavity and decided to perform the further treatment by using both accesses. Endoscopic debridement was repeated daily through the transgastric as well as the transduodenal approach over 5 days. The clinical condition of the patient dramatically improved and he became afebrile. Two months after the initial endoscopic necrosectomy, a CT scan showed nearly complete resolution of the pancreatic necrosis and the bile duct stenosis resolved. Six months later, CT scans showed no residual necrosis and an atrophic but otherwise normal pancreas [222].

Step-up approach

Necrotizing pancreatitis with infected necrotic tissue is associated with a high rate of complications and death. Standard treatment is open necrosectomy. The outcome may be improved by a minimally invasive step-up approach. In a multicenter study, it was randomly assigned 88 patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue to undergo primary open necrosectomy or a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The primary end point was a composite of major complications (new-onset multiple-organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death. The primary end point occurred in 31 of 45 patients (69 %) assigned to open necrosectomy and in 17 of 43 patients (40 %) assigned to the step-up approach (risk ratio with the step-up approach, 0.57; 95 % confidence interval 0.38 to 0.87), which was a significant difference. Of the patients assigned to the step-up approach, 35 percent were treated with percutaneous drainage only. New-onset multiple-organ failure occurred significantly less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12 % vs 40 %). The rate of death did not differ significantly between groups (19 % vs 16 %). Patients assigned to the step-up approach had a significantly lower rate of incisional hernias (7 % vs 24 %) and new-onset diabetes (16 % vs 38 %). It was concluded that a minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite end point of major complications or death among patients with necrotizing pancreatitis and infected necrotic tissue [223].

Retroperitoneal necrosectomy

Comparison of minimal access retroperitoneal pancreatic necrosectomy (MARPN) versus open necrosectomy in the treatment of infected or nonresolving pancreatic necrosis was done in a retrospective analysis on a prospective data base comprising 189 consecutive patients undergoing MARPN or open necrosectomy (1997 to 2008). Outcome measures included total and postoperative ICU and hospital stays, organ dysfunction, complications and mortality using an intention to treat analysis. Overall 137 patients underwent MARPN versus open necrosectomy in 52. Median (range) age of the patients was 56 (18-85) years; 118 (62 %) were male. A total of 131 (69 %) patients were tertiary referrals, with a median time to transfer from index hospital of 19 (2-76) days. Etiology was gallstones or alcohol in 129 cases (68 %); 98 of 168 (58 %) patients had a positive culture at the first procedure. Of the 137 patients, 34 (31 %) had postoperative organ failure in the MARPN group, and 39 of 52 (56 %) in the open group, which was a significant difference; 59/137 (43 %) versus 40/52 (77 %), respectively, required postoperative ICU support, which also was a significant difference. Of the 137 patients 75 (55 %) had complications in the MARPN group and 42 of

52 (81 %) in the open group – a significant difference. There were 26 (19 %) deaths in the MARPN group and 20 (38 %) following open procedure, again a difference. Age, preoperative multiorgan failure, and surgical procedure (MARPN) were significant independent predictors of mortality. The authors concluded that the study has shown significant benefits for a minimal access approach including fewer complications and deaths compared with open necrosectomy [224].

Retroperitoneal drainage

In infected pancreatic necrosis it was used the “pipe-organ”-like retroperitoneal drainage, which is usually used in the management of open pelvic fracture, successfully in a patient with severe infected pancreatic necrosis. This procedure can avoid gastrointestinal fistula and local bleeding without necessitating surgery [225].

Disconnected left pancreatic remnant

Disconnected left pancreatic remnant (DLPR) presents clinically as a pancreatic fistula, pseudocyst, or obstructive pancreatitis. Optimal operative treatment, either distal pancreatectomy (DP) or internal drainage (ID), remains unknown. One paper critically evaluated operative experiences in patients with DLPR in a retrospective analysis of a consecutive case series from a single, high-volume institution. A total of 76 patients with radiographic-confirmed DLPR (CT + ERCP or MRI) who had operations between 1995 and 2008 were included. Pancreas preservation (the use of ID) was the default unless anatomic, physiologic, or technical factors precluded it. Follow-up to 2009 was done (median follow-up, 22 months). The mean age of this cohort was 52 years (range, 18-85); 57 percent of the patients were male. A total of 59 (73 %) had acute pancreatitis, whereas 17 (22 %) had chronic pancreatitis. Presentation was pseudocyst in 53 percent, pancreatic fistula in 34 percent, and obstructive pancreatitis in 13 percent. Resection (DP) and drainage (ID) options were utilized equally for each clinical presentation as follows: pseudocyst, 60/40; pancreatic fistula, 50/50; or obstructive pancreatitis, 50/50. The strongest driver for DP (92 %) was a small pancreatic remnant and splenic vein thrombosis. In contrast, large pancreatic remnants had ID 70 percent of the time. No differences in short- or long-term outcomes between DP or ID options were identified. It was concluded that by using anatomic, physiologic, and technical factors to guide operative choice in DLPR, it was report a 74 percent success rate with distal pancreatectomy and an 82 percent success rate with internal drainage at a median follow-up of 22 months. A pancreatic remnant size >6 cm favored internal drainage options over resection [226].

Hemorrhage in acute pancreatitis

Haemorrhage is a rare, potentially fatal complication in acute pancreatitis (AP). The aim was to investigate the incidence, management and outcome related to this complication. The medical records of all patients with AP who presented to a single hospital between 1994 and 2009 were reviewed retrospectively. Patients who developed at least one in-hospital episode of major haemorrhage were selected. The etiology, patient characteristics, occurrence of sentinel bleeding, clinical management and outcome were recorded. Fourteen (1.0 per cent) of 1356 patients diagnosed with AP developed major haemorrhage. Angiography established the diagnosis in four of six patients. Embolization was successful in one patient. Surgery was performed in two patients. Sentinel bleeding occurred in three of four patients with major postoperative bleeding. The overall mortality rate was 36 percent (5 of 14 patients). Haemorrhage presenting after more than 7 days was associated with a higher mortality rate of 80 per cent (4 of 5 patients). A fatal outcome was at least three times more likely in

patients with severe AP and haemorrhagic complications than in those with severe AP but no bleeding. It was concluded that major hemorrhagic complications of AP are rare, but clinically important. Major postoperative bleeding is often preceded by sentinel bleeding. Intra-abdominal hemorrhage presenting more than 1 week after disease onset is a highly fatal complication [227].

Peritoneal lavage

The use of peritoneal lavage in patients with acute pancreatitis remains controversial. While recent guidelines do not make a positive recommendation for its use, there continues to be reports of clinical benefits from peritoneal lavage in this setting. The aim of one study was to systematically review the available randomized controlled trials of peritoneal lavage in patients with severe acute pancreatitis. The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and four major Chinese biomedical databases were searched. A random effects model was used in meta-analysis. The summary estimates were reported as risk ratios (RR) with corresponding 95 percent confidence interval. Ten randomized controlled trials, encompassing a total of 469 patients, were included. When compared with conservative treatment, the use of peritoneal lavage did not result in a statistically significant difference in the risk of mortality (RR 0.82; 95 % confidence interval 0.32 to 1.79) or complications (RR 1.33; 95 % confidence interval 0.99 to 2.12). The use of peritoneal lavage with antiproteases, in comparison with peritoneal lavage only, also did not result in a statistically significant difference in the risk of mortality and complications. Thus it was concluded that lavage of the peritoneal cavity in patients with severe acute pancreatitis does not appear to confer a clinical benefit. Whether lavage of the pancreatic bed after necrosectomy is beneficial has yet to be determined [228].

Nutrition in acute pancreatitis

Nutritional concepts in acute pancreatitis have changed. Early enteral nutrition widely replaced parenteral nutrition alone in severe acute pancreatitis. First trials suggest early oral refeeding as nutritional treatment of choice in patients with mild acute pancreatitis. In one review, it was summarise the current knowledge on nutrition in acute pancreatitis and discussed future developments [229].

Enteral nutrition

A systematic review was carried out to analyze current evidence-based data on the use of enteral nutrition in the management of acute pancreatitis. Literature search was performed on "Pubmed" and "Medline" databases to identify articles investigating the role and potential effect of enteral nutrition on the outcome of patients with acute pancreatitis. Relevant data were analyzed from the viewpoints of possible benefits and complications, route and timing of administration, and composition of nutrients. Thirty-two prospective randomized controlled trials and 15 meta-analyses of those were identified and included in the overview. Strong evidence suggests that enteral nutrition significantly reduces mortality rate of severe acute pancreatitis. While both nasogastric and nasojejunal feeding appear to be safe in severe pancreatitis, early low-fat oral diet is possibly beneficial in patients with mild pancreatitis. Since maintenance of the gut barrier function is one of the crucial effects of enteral nutrition, enteral feeding should be commenced within the first 24 h after hospital admission, in order to prevent early bacterial translocation. However, it seems that neither immunoenhanced nutrients nor probiotic supplementation are able to reduce mortality further, and – therefore – cannot be recommended for patients with acute pancreatitis. Although enteral nutrition is undoubtedly a key component of the management of acute pancreatitis, the exact role of that

is needed to be defined yet. In particular, conflicting data from studies on nutrient compositions will require further clarification in the future [230].

Nutrition in severe acute pancreatitis is a critical aspect in the management of this condition. One review aimed to systematically review the evidence available to inform the use of nutritional support in severe acute pancreatitis. High quality (level 1) evidence supports naso-jejunal enteral nutrition (NJ-EN) over parenteral nutrition (PN) reducing infectious morbidity and showing a trend towards reduced organ failure although there is no detectable difference in mortality. Trial data may underestimate benefit as patients are often recruited with predicted rather than proven severe disease. NJ-EN is safe when started immediately (level 3 evidence). NJ-EN is often impractical and naso-gastric (NG) feeding seems to be equivalent in terms of safety and outcomes whilst being more practical (level 2 evidence). Regarding feed supplementation, probiotic feed supplementation is not beneficial (level 1 evidence) and may cause harm with excess mortality (level 2 evidence). No evidence exists to confirm benefit of the addition of prokinetics in severe acute pancreatitis (SAP) although their use is proven in other critically ill patients. Level 2 evidence does not currently support the use of combination immuno-nutrition though further work on individual agents may provide differing results. Level 2 evidence does not support intravenous supplementation of anti-oxidants and has demonstrated that these too may cause harm [231].

Enteral nutrition (EN) reduces infectious complications and mortality compared with parenteral nutrition (PN) in patients with predicted severe acute pancreatitis. However, to date the complications attributable to the administration of EN and PN in this patient group have not been comprehensively studied. The aim of one study was to systematically review the complications related to the use of nutrition in patients with predicted severe acute pancreatitis receiving EN versus PN. The Cochrane Library, MEDLINE and Scopus were searched. Randomised controlled trials (RCT) of EN versus PN in predicted severe acute pancreatitis were selected. Data from five RCT were meta-analysed. Diarrhoea occurred in six of ninety-two (7 %) patients receiving PN and twenty-four of eighty-two (29 %) patients receiving EN (odds ratio 0.20; 95 % confidence interval 0.09 to 0.43). Hyperglycaemia developed in twenty-one of ninety-two (23 %) patients receiving PN and nine of eighty-two (11 %) receiving EN (odds ratio 2.59; 95 % confidence interval 1.13 to 5.94). Given a significant reduction in infectious complications and mortality associated with the use of EN over PN that has been consistently demonstrated in previous studies, the former should be the treatment of choice in acute pancreatitis [232].

Enteral versus parenteral nutrition

One study was designed to evaluate the effects of total enteral nutrition and total parenteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. One hundred seven patients were enrolled in the study between 2003 and 2007. In the first week of hospitalization, they were randomized to feeding by either total parenteral nutrition (54 patients) or total enteral nutrition (53 patients). All patients were concomitantly administered with sufficient prophylactic antibiotics. Computed tomographic scan and C-reactive protein level indicated a similar clinical severity in both groups. Eighty percent of the patients developed organ failure in the group with total parenteral nutrition, which was higher than that in the group with total enteral nutrition (21 %). Eighty percent and 22 percent of the patients in the total parenteral nutrition and total enteral nutrition groups, respectively, underwent surgical intervention. The incidence of pancreatic septic necroses in the group with total enteral nutrition (23 %) was lower than that in the group with total parenteral nutrition (72 %). Mortality in the total parenteral nutrition group (43 %) was higher than in the total enteral nutrition group (11 %). It was concluded that total enteral nutrition is better than total parenteral nutrition in the prevention of pancreatic necrotic infection in severe acute pancreatitis [233].

Abdominal compartment syndrome

One study investigated the effects of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) on gut barrier function in critically ill surgical patients. A prospective observational cohort study on patients with severe acute pancreatitis or abdominal sepsis admitted to an intensive care or high-dependency unit and intra-abdominal pressure (IAP) and plasma levels of immunoglobulin G (IgG) and IgM antiendotoxin core antibodies (EndoCAb) and procalcitonin (ProCT) were measured serially. Among 32 recruited patients, 24 (75 %) and 8 patients (25 %) developed IAH and ACS, respectively. The state of ACS was associated with significant reductions in plasma IgG EndoCAb and IgM EndoCAb and higher concentrations of plasma ProCT compared with absence of ACS. Resolution of IAH and ACS was associated with significant recovery of plasma IgG EndoCAb and IgM EndoCAb and reduction in plasma ProCT concentration. Negative correlations were observed between IAP and plasma IgG EndoCAb and IgM EndoCAb. It was concluded that intra-abdominal hypertension and ACS are associated with significantly higher endotoxin exposure and ProCT concentrations, suggestive of gut barrier dysfunction. Resolution of intraabdominal hypertension and abdominal compartment syndrom is associated with evidence for recovery of gut barrier function [234].

Acute pancreatitis in young adults

The etiology of acute pancreatitis seems to have changed during the last two decades, and since detection of mutations in the gene for cationic trypsinogen (PRSS1) causing hereditary pancreatitis some patients formerly diagnosed with idiopathic AP (IAP) turn out to have a genetic cause. Data on patients <30 years of age, diagnosed with AP identified in the Danish National Registry of Patients, were retrieved. Patients previously diagnosed with IAP were offered genetic counseling and testing for mutations in the PRSS1, the Serine Protease Inhibitor Kazal type1 (SPINK1) and the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR). The standardized incidence ratio (SIR) of AP increased from 3.56 per 100,000 person-years in the period 1980-1984 to 6.43 in 2000-2004, which is a statistically significant difference. The SIR of women surpassed that of men in 1999. Among patients with former IAP, 3 had hereditary pancreatitis, 3 CFTR and 4 SPINK1 mutations after re-evaluation. The authors concluded that the incidence of AP, especially in women, increased over time. More patients had gallstone-related and less alcohol-related AP in the period 1999-2004 compared to 1980-1999. Genetic causes of acute pancreatitis were found in 32 percent of those tested with IAP and as a minimum estimation in 4 percent of the total cohort [235].

Acute pancreatitis in children

Studies have shown an increased incidence of adult acute pancreatitis in recent decades. The aim of one study was to review pediatric incidence of acute pancreatitis. A retrospective review of computerized databases at a children's hospital from 1993 to 2004 was performed. The International Classification of Diseases, Ninth Revision, code 5770 Acute Pancreatitis was used; results were tabulated by discharge year and month. The incidence of acute pancreatitis was compared with orders for amylase and lipase testings and with the catchment population. Over the study period, there were a total of 1021 discharge diagnoses of acute pancreatitis (731 first diagnoses). The diagnosis of pancreatitis increased from a low of 28 total cases (21 first diagnoses) in 1993 to a high of 141 total cases (109 first diagnoses) in 2004. The catchment population decreased from 882,000 to 826,500. The estimated incidences of first acute pancreatitis admission were 2.4 to 13.2 per 100,000 children. Linear

regression analysis suggests that increased testing for amylase and lipase could account for 94 percent of the change in all pancreatitis admissions [236].

Acute recurrent pancreatitis in children can be caused by anomalies of fusion of pancreatic ducts such as the dominant dorsal duct syndrome wherein a dominant dorsal pancreatic duct is associated with stenosis of the minor papilla. Clinical presentations and management of 2 patients were discussed. An infant presented with severe acute pancreatitis with pseudocyst formation due to an underlying ductal disruption. Surgical treatment was offered on account of failure of medical therapy and endoscopic stenting. A dominant dorsal duct with minor papilla stenosis was encountered. Sphincteroplasty of the minor papilla and lateral pancreaticojejunostomy were performed with good result. A 14-year-old boy with a type 1 choledochal cyst was troubled by recurrent acute pancreatitis. At operation, a dilated dorsal pancreatic duct opening into a stenosed minor papilla was found in addition to the choledochal cyst. Choledochal cyst excision, choledochoduodenostomy, and sphincteroplasty of the minor papilla stenosis were performed. Dominant dorsal duct syndrome is a rare cause of acute pancreatitis in children. A high index of suspicion is necessary to establish a precise diagnosis. Sphincteroplasty of the minor papilla may affect adequate pancreatic drainage and prevent recurrent pancreatitis [237].

Mumps

Mumps is a contagious disease commonly characterized by nonsuppurative parotitis as a result of an acute viral infection. Before the development of mumps vaccination, this was a common disease of childhood and in rare circumstance may involve the testicles causing orchitis and the brain causing meningitis. Viral replication occurs in the epithelial lining of the upper respiratory tract. Viremia may lead to systemic dissemination, hence, involvement of other major organs. Pancreatitis arises in approximately 4 percent of mumps infections and commonly occurs in children or young adults. It was reported a case of acute pancreatitis as a result of nonparotid involving mumps infection in an unvaccinated elderly patient to reiterate important differential etiologies in nonalcoholic and nonbiliary pancreatitis. The result of the mumps serological test was positive for enzyme immunoassay mumps IgM antibodies and negative for mumps IgG antibodies consistent with an acute mumps infection. The parotids and testicles were examined and were negative for any swelling or signs of inflammation. The patient improved clinically on treatment over a period of 5 days and was discharged on day 6. Pancreatitis in association with mumps has been reported way back in the 1940s. It may occur in individuals undergoing vaccination with the measles, mumps, and rubella vaccine, individuals with impaired host immune system, and those in the pediatric population [238].

Case reports

Lymphoma as a cause of acute pancreatitis

It was presented a case of primary lymphoma of the common bile duct presenting with acute pancreatitis and cholangitis [239].

Hypertriglyceridemia

Hypertriglyceridaemia is an uncommon cause of acute pancreatitis, accounting for 1-4 percent of cases. In the case of lipoprotein-lipase mutations, lipid levels may rise to extreme levels during acute pancreatitis. In this case a 29-year-old female was hospitalized several times due to acute pancreatitis. She presented with extreme lipid levels and difficulty in blood

testing. While the correlation of acute pancreatitis and hyperlipidaemia is known, awareness of its association with defects in lipid metabolism could, in this case, have furthered diagnostic and prevented repeated hospitalizations [240].

Inferior vena cava thrombosis

A 21-year-old man admitted complaining of sudden severe epigastric pain for 1 day. He had been diagnosed as ulcerative colitis (UC) and taking mesalazine for two months. UC was in nearly complete remission at admission. He never drank an alcohol, and serum amylase was 377 IU/L. CT scan showed inferior vena cava (IVC) thrombosis in addition to mild acute pancreatitis. To evaluate the cause of acute pancreatitis and IVC thrombosis, magnetic resonance cholangiopancreatogram (MRCP), endoscopic ultrasonogram (EUS), lower extremity Doppler ultrasonogram (US) and blood test of hypercoagulability including factor V, cardiolipin Ab, protein C, protein S1, antithrombin III, and anti phospholipids antibody were performed. There was no abnormality except mild acute pancreatitis and IVC thrombosis in all the tests. He was recommended to stop taking mesalazine and start having anticoagulation therapy. After all symptoms disappeared and amylase returned normal, rechallenge test with mesalazine was done. Flare-up of abdominal pain occurred and the elevation of serum amylase was observed. Ulcerative colitis came to complete remission with short-term steroid monotherapy. Acute pancreatitis and IVC thrombosis were completely resolved after 3-month anticoagulation therapy with no more mesalazine. It was postulated that IVC thrombosis occurred due to hypercoagulable status of UC and intra-abdominal inflammation caused by mesalazine-induced pancreatitis [241].

Experimental

Activated protein C

Activated protein C (APC) is increasingly understood to have diverse regulatory functions in inflammation. However, the exact mechanism of action remains unclear in severe acute pancreatitis (SAP). The aim of one study was to demonstrate the effects of APC on expressions of thrombomodulin (TM) and endothelial cell protein C receptor (EPCR), and its subsequent effect on the severity of SAP. Sprague-Dawley rats were randomly divided into four groups. The rats were given intravenous injections of APC (50, 10 microg/kg, respectively, treated groups) or saline (SAP group) just before induction of SAP. One group of rats underwent only sham operation as control group. Experimental samples were harvested at 16 h after induction. The protein and mRNA levels of matrix metalloprotease 9 (MMP-9), TM, and EPCR in pancreatic tissue were investigated. Serum tumor necrosis factor alpha (TNF-alpha) and interleukin-8 (IL-8) levels were determined. The severity of disease was evaluated by histological score of pancreatic injury, wet/dry weight ratio of pancreatic tissue, and serum amylase. In the APC 50 microg/kg-treated group, serum TNF-alpha, IL-8, and pancreatic MMP-9 levels were decreased and the levels of pancreatic EPCR and TM were up-regulated compared with the SAP group. A significant dose-dependent relationship was found between the decreased levels of serum IL-8 and the APC-treated dosage. Furthermore, the severity of SAP was ameliorated by APC treatment. It was concluded that APC could augment the anti-coagulation and anti-inflammatory activity by up-regulating EPCR and TM expressions, thus attenuating the severity of SAP [242].

Carbon dioxide

It was investigated the effect of CO₂ pneumoperitoneum on the local and systemic inflammatory response in acute pancreatitis induced in Wistar rats by 5 percent taurocholate intraductal injection. Carbon dioxide pneumoperitoneum was applied for 30 minutes before

the induction of acute pancreatitis. Inflammatory parameters were evaluated in the peritoneum (ascites, cell number, and tumor necrosis factor-alpha, TNF-alpha), serum (amylase, TNF-alpha, interleukin-6, and IL-10), pancreas (myeloperoxidase, MPO, activity, cyclo-oxygenase 2 and inducible nitric oxide synthase expression, and histological diagnosis), liver, and lung (mitochondria dysfunction and MPO activity). It was found that abdominal insufflation with CO₂ before induction of acute pancreatitis caused a significant decrease in ascites volume, cells, and TNF-alpha in the peritoneal cavity and in serum TNF-alpha and IL-6 but not IL-10 levels. In the pancreas, this treatment reduced MPO activity, acinar and fat necrosis, and the expression of inducible nitric oxide synthase and cyclo-oxygenase 2. There were no significant differences on serum amylase levels, liver mitochondrial function, and pulmonary MPO between groups. The data demonstrated that CO₂ pneumoperitoneum reduced pancreatic inflammation and attenuated systemic inflammatory response in acute pancreatitis in the rat [243].

Leflunomide treatment?

Nuclear factor-kappaB is a potent mediator in several steps of acute pancreatitis. Leflunomide is a novel immunomodulating drug that is also a potent inhibitor of nuclear factor-kappaB activation. The aim of one study was to investigate the effects of leflunomide pretreatment in severe necrotizing pancreatitis in rats. Fifty rats were randomly divided into 5 groups. Severe necrotizing pancreatitis was induced by retrograde injection of 3 percent sodium taurocholate into the common biliopancreatic duct. Leflunomide (10 mg/kg) was given intragastrically for 2 doses before the experiment. Serum amylase activity, pancreatic histopathologic condition, malondialdehyde level, myeloperoxidase enzyme activity, nitric oxide level, and pulmonary changes were assessed. Leflunomide pretreatment significantly ameliorated pancreatic hemorrhage, edema, and neutrophil infiltration and decreased histopathological score compared with the untreated severe necrotizing pancreatitis group. Change in pulmonary alveolar distention was significant. Although serum amylase levels also decreased, the difference was not significant. Thus, leflunomide is a beneficial agent in the severe form of acute pancreatitis in rats [244].

Peritoneal lavage

Intraperitoneal administration of trypsin stimulates the production of cytokines from peritoneal macrophages. Removing the pancreatitis-associated ascitic fluid from the peritoneal cavity may decrease the systemic inflammatory response in acute pancreatitis (AP). It was investigated the effect of peritoneal lavage on the systemic inflammatory response in severe AP. Acute pancreatitis was induced in Wistar rats by 5 percent taurocholate intraductal injection. Peritoneal lavage was performed for 4 hours after onset of AP. At 4 hours after induction of AP, serum samples were assayed for amylase and inflammatory cytokines: tumor necrosis factor (TNF-alpha), interleukin-6 (IL-6), and IL-10. Expression of pancreatic cyclooxygenase-2 and inducible nitric oxide synthase, liver mitochondrial function, and pulmonary myeloperoxidase activities were determined. Peritoneal lavage after AP led to a decrease in serum levels of tumor necrosis factor-alpha and IL-6 and an increase in IL-10. In the pancreas, this treatment reduced cyclooxygenase-2 and inducible nitric oxide synthase expression. Liver mitochondrial dysfunction was also reduced. There were no differences on serum amylase levels and pulmonary myeloperoxidase between groups with AP. It was concluded that peritoneal lavage has a systemic anti-inflammatory effect in severe acute pancreatitis [245].

CHRONIC PANCREATITIS

The diagnosis of chronic pancreatitis is based on a typical history with recurrent flares of acute inflammation, imaging procedures and some laboratory tests. Using imaging procedures (abdominal ultrasound, computed tomography or magnetic resonance imaging), a diagnosis can only be made when alterations in size (enlargement or atrophy) or shape of the pancreas or changes in intrapancreatic structure (dilation, obstruction of ducts), calcifications, or changes in peripancreatic organs have occurred. Tests of exocrine pancreatic function are not essential for making a diagnosis of chronic pancreatitis [246].

Classification

Chronic pancreatitis (CP), defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes which typically cause abdominal pain and/or permanent impairment of pancreatic function, has proved resistant to categorization. The disease may present clinically either with an individual symptom or a combination of symptoms associated with loss of pancreatic function. The single most frequent symptom of CP is pain, either in the form of intermittent episodes or in a more chronic or persistent pattern. The natural history of CP is usually characterized by progression of tissue damage and various degrees of exocrine and endocrine pancreatic insufficiency, which will become apparent over time. The main reason for the lack of guided strategies in the therapeutic management of CP is the absence of a clinically applicable classification of CP. In the past, several classifications have certainly contributed to a better understanding of the pathogenesis and pathophysiology of CP. The meetings in Marseilles (1963 and 1984), Cambridge (1984) and in Rome (1985) added a great deal of information to our knowledge of the pathogenesis and evolution of CP. More recent work on understanding the temporal course of CP led to the Zurich international classification which has been used to define patient cohorts in recent studies of patients undergoing surgery for CP. In order to combine clinical experience in the field of CP with progress in diagnostic methods and new molecular technologies for the assessment of CP, a classification of CP based on key clinical aspects is crucial. A new classification should first be validated to determine whether it can be applied to the majority of patients with CP, and then the value of such a classification needs to be tested in our understanding of the natural course in different etiologies (progression, arrest, regression) and most importantly, to study the clinical outcome when different therapeutic strategies are applied [247].

Epidemiology and etiology

Cigarette smoking is a dose-dependent risk factor for acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis. A minority of chronic alcohol consumers develop recurrent acute pancreatitis but very heavy drinking associates with chronic pancreatitis. More patients with alcohol-induced chronic pancreatitis have cirrhosis than patients with cirrhosis have chronic pancreatitis (39 % vs 18 %). Most patients with asymptomatic hyperenzymemia have no pancreatic lesions. Pancreatic calcifications are most frequently due to chronic pancreatitis, followed by cystic neoplasms and other disorders. The new Rosemont consensus classification of endoscopic ultrasonography criteria for chronic pancreatitis is unvalidated. Zinc deficiency correlates only with severe chronic pancreatitis and the fecal elastase test is an inaccurate marker of pancreatic steatorrhea. Patients commonly receive insufficient lipase to abolish pancreatic steatorrhea. Ultrastructural neuropathies are common to chronic pancreatitis and pancreatic cancer and correlate with pain severity. These facts further elucidated risk factors for pancreatic disease, the natural

history of alcoholic pancreatitis, the differential diagnosis of pancreatic calcifications, the diagnosis of chronic pancreatitis with the Rosemont criteria, the limited diagnostic utility of fecal elastase test and zinc measurements, the proper dosing of pancreatic enzyme supplements, and treatment of pancreatic pain [248].

In the past, chronic pancreatitis has been regarded as a fairly uniform and largely untreatable disorder that most commonly affects patients who both lack gainful employment or adequate insurance coverage and have a tendency to smoke and drink. Large clinical trials suggest that this perception is not only misguided and discriminatory but also not based on facts. It was forgotten that the perception of chronic liver disease was similar before World War II, and just like liver cirrhosis the fibrosis and cirrhosis of the pancreas – i.e. chronic pancreatitis – is the end result of a range of environmental, inflammatory, infectious and genetic disorders. A growing number of these have only recently been recognized as a distinct entity and several of which are becoming truly treatable. A large proportion of the risk for developing pancreatitis is conveyed by genetic risk factors, and we estimate that less than half of those have been identified so far. The same holds true for protective factors that can prevent pancreatitis, even in the face of excessive alcohol abuse. Various gene mutations and polymorphisms appear to determine an individual's susceptibility for developing pancreatic disease, for the severity of the disease, and for the disease progression. The spectrum of genotype/phenotype associations ranges from straightforward autosomal dominant traits with near-complete penetrance, as for the most common mutations in the cationic trypsinogen gene (PRSS1), to moderate risks factors without mendelian inheritance patterns, as for SPINK1 and CFTR mutations, to very subtle risk associations and disease modifiers that can only be identified in large cohort studies, as for the chymotrypsin C, calcium-sensing receptor and the anionic trypsin (PRSS2) mutations. Only a better understanding of the disease mechanisms that underlie these changes will make an individualized therapy of pancreatic disorders a realistic option [249].

Publications on etiology of chronic pancreatitis (CP) are infrequent. Etiologies today encompass genetic disorders. It was described etiologies of today and identify patients with genetic disorders like hereditary pancreatitis (HP), mutations in Serine Protease Inhibitor Kazal type1 (SPINK1), and the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR) among patients formerly considered to have idiopathic CP. Data on patients diagnosed with first-time CP < 30 years of age in Denmark identified in the Danish National Registry of Patients were retrieved. Patients previously considered to have idiopathic pancreatitis were offered genetic counseling and evaluation for HP, SPINK1, and CFTR mutations. In the period 1980-2004, 580 patients < 30 years of age presented with CP, the standardized prevalence ratio of CP increased from 12 per 100,000 person years in 1980-1984 to 17 per 100,000 in 2000-2004, which was a significant difference. The odds ratio (OR) having gallstone-related CP increased in the latter time period, especially in women, that of alcohol-induced CP decreased over time. OR having idiopathic CP increased in the latter period; 50 percent of patients with idiopathic pancreatitis accepted genetic reevaluation; 28 patients had a genetic mutation that totally or partly could explain their pancreatitis, nine of these had two, and 11 patients had HP. It was concluded that the prevalence of CP, especially in women, increased over time. Genetic causes that partly or totally could explain the CP were found in 55 percent (95 % confidence interval 40 to 69) of those with idiopathic chronic pancreatitis, as a minimum estimation 1.9 percent (95 % confidence interval 1.0 to 3.5) of the total cohort had hereditary pancreatitis [250].

Survival

It was investigated mortality of patients with chronic pancreatitis (CP), compared with the Danish population and sought to determine whether clinical presentations of CP can be used in prognosis. It was also investigated clinical factors associated with mortality and causes of death among these patients. The Copenhagen Pancreatitis Study is a prospective study of

patients admitted from 1977 to 1982 to the five main hospitals in Copenhagen with a diagnosis of acute pancreatitis or CP. In 2008, follow-up data were collected from these patients from the Danish Registries; this subcohort comprised 290 patients with probable (n=41) or definite chronic pancreatitis (n=249). The mortality of patients with definite CP was 4-fold that of the Danish population and significantly higher than that of patients with probable CP (95 % confidence interval 1.21 to 2.57); patients with probable CP had a 2- to 3-fold higher mortality rate than the population. In patients with definite CP, factors significantly associated with mortality included non-employment (95 % confidence interval 0.53 to 0.93), and being underweight (95 % confidence interval 0.52 to 0.95). Gender, alcohol use, smoking, single versus co-living, exocrine insufficiency, diabetes, pancreatic calcification, CP inheritance, painless CP, acute exacerbation of CP, or surgery for CP had no impact on survival. The most frequent causes of death were digestive diseases (20 %), malignancies (20 %), and cardiovascular diseases (11 %) [251].

Smoking

It is not completely understood whether smoking contributes to chronic pancreatitis. Past studies have included mostly patients with alcohol-related and severe chronic pancreatitis. The aim of one study was to assess the relationship of smoking and chronic pancreatitis adjusting for alcohol and other clinical risk factors. A cross-sectional study was performed of patients referred to the pancreatic disease clinic in the past two years with abdominal pain and suspected chronic pancreatitis. Patients were questioned on their smoking and alcohol habits. Patients underwent an etiological workup and diagnostic evaluation for early and late chronic pancreatitis comprised of computed tomography scan and combined endoscopic ultrasound and secretin endoscopic pancreatic function test if indicated. Logistic regression was used to determine the association of current smoking with chronic pancreatitis adjusting for other risk factors. The adjusted odds ratio for current smoking was 1.99 (95 % confidence interval 1.01 to 3.91). Other significant predictors included consumption of >10 alcohol drinks/week, advancing age, history of acute pancreatitis, and the presence of another etiological factor. Smoking was also independently associated with exocrine insufficiency (odds ratio 2.00, 95 % confidence interval 1.07 to 3.75) and calcifications (odds ratio 2.68, 95 % confidence interval 1.03 to 6.94). It was concluded that active cigarette smoking is associated with chronic pancreatitis adjusting for alcohol and other risk factors [252].

To assess the evidence for tobacco smoking as a risk factor for the causation of chronic pancreatitis it was performed a meta-analysis with random-effects models to estimate pooled relative risks (RRs) of chronic pancreatitis for current, former, and ever smokers, in comparison to never smokers. It was also performed dose-response, heterogeneity, publication bias, and sensitivity analyses. Ten case-control studies and 2 cohort studies that evaluated, overall, 1705 patients with chronic pancreatitis satisfied the inclusion criteria. When contrasted to never smokers, the pooled risk estimates for current smokers was 2.8 (95 % confidence interval 1.8 to 4.2) overall and 2.5 (95 % confidence interval 1.3 to 4.6) when data were adjusted for alcohol consumption. A dose-response effect of tobacco use on the risk was ascertained: the RR for subjects smoking less than 1 pack per day was 2.4 (95 % confidence interval, 0.9 to 6.6) and increased to 3.3 (95 % confidence interval 1.4 to 7.9) in those smoking 1 or more packs per day. The risk diminished significantly after smoking cessation, as the RR estimate for former smokers dropped to a value of 1.4 (95 % confidence interval 1.1 to 1.9) [253].

Obesity

Obesity is a known risk factor for severe acute pancreatitis. Since alcoholic chronic pancreatitis (ACP) is closely linked to alcoholic AP, overweight before disease onset might impact on incidence and outcome of ACP, and represent an additional risk factor for ACP.

This issue has not been investigated, despite discussions on the “hypercaloric-high-fat” hypothesis as an additional risk factor for ACP for many years. The study is part of a prospective long-term study of a large, mixed, medical/surgical series of ACP patients. All cooperative patients were studied according to a protocol regarding clinical symptoms, physical status, routine laboratory tests, pancreatic function and pancreatic morphology (e.g. calcification) at yearly follow-ups. The study included 227 ACP patients with recorded body mass index (BMI) before disease onset followed up on average for 18 years from chronic pancreatitis (CP) onset. Males predominated (90 %), age at onset averaged at 36 years, and exocrine insufficiency (97 %) and calcification (88 %) developed in virtually all patients. Surgery for B-type pain was performed in 58 percent, and death occurred in 63 percent. Overweight before disease onset was found in 54 percent (obesity in 15 %) compared to 38 percent (3 %) from a contemporary male control population. The highest BMI before disease onset did not impact on some major variables of ACP such as gender, age, progression of exocrine insufficiency, diabetes and calcification, and mortality from CP, except for a delayed progression rate of ACP indices in the surgical series. Thus, overweight before disease onset appears to be another risk factor for ACP, supporting the ‘hypercaloric-high-fat’ hypothesis [254].

Oxidative stress

One review presented new evidence on the role of oxidative stress and antioxidant status in acute and chronic pancreatitis published in the last year. In-vitro studies showed that protein phosphatases may play an important role in the interaction between reactive oxygen species and proinflammatory cytokines in acute pancreatitis. In-vivo studies found that several natural compounds ameliorate oxidative stress and, therefore, have therapeutic potential. In the domain of clinical studies, the major development is the first double-blind placebo-controlled randomized trial that showed effectiveness of oral antioxidant supplementation (organic selenium, ascorbic acid, alpha-tocopherol, beta-carotene, and methionine) in relieving pain in patients with chronic pancreatitis. The developments in clinical studies on acute pancreatitis are less spectacular and mainly limited to evaluation of different markers of oxidative stress and antioxidant status in the course of disease. It was concluded that a significant advance has been made in the arena of research in chronic, but not acute, pancreatitis. There is now solid evidence to justify the use of oral antioxidants in the treatment of patients with chronic pancreatitis. The progress in clinical research on antioxidants in acute pancreatitis is hampered by several factors, including suboptimal classification of acute pancreatitis and route of administration used in previous studies [255].

Trace elements

One study evaluated the degree to which the levels of trace elements, copper, iron, selenium, zinc and hemoglobin-Fe³⁺ in blood, serum and pancreas have any role to play in the calcification process associated with fibrosis in pancreas. Twenty-seven calcific (CCP) and 23 non-calcific chronic pancreatitis (CP) patients and equal number of age- and sex-matched normal volunteers (50) were enrolled in the study. Surgically removed pancreatic tissue and blood samples were analysed for copper, iron, selenium, zinc, protein, collagen and lipid peroxidation products in terms of malondialdehyde, protein carbonyls, glutathione, methemoglobin, methemoglobin reductase and ceruloplasmin activity levels. It could be found that the pancreatic tissue levels of copper, iron, protein and collagen contents were significantly elevated in CCP patients when compared to CP patients. Serum levels of copper, free ionic copper and iron were also elevated in CCP patients. The serum and the pancreatic tissue level of zinc and selenium showed a significant decrease in CCP patients. The level of methemoglobin was elevated more significantly with the concomitant decline in the activity of methemoglobin reductase. There was a positive correlation between the pancreatic level of copper and iron with the collagen and protein levels. The results of the present study revealed that the levels of copper and iron, the pro-oxidants and zinc and

selenium may influence calcification process in CCP patients. Hypoxia-related tissue injury due to the formation of oxidised hemoglobin may also contribute to the pathogenesis of calcification in pancreas [256].

Genetics

Proinflammatory cytokines, such as tumour necrosis factor alpha (TNFalpha), play fundamental roles in the pathogenesis of acute pancreatitis (AP). The aim of one study was to determine if polymorphisms in the TNFalpha gene are associated with AP. Two polymorphisms located in the promoter region (positions -308 and -238) in TNFalpha gene were determined using polymerase chain reaction- (PCR-) restriction fragment length polymorphism (RFLP) methods in 103 patients with AP and 92 healthy controls. Odds ratios (ORs) were estimated using logistic regression analysis adjusted for age, sex, BMI and smoking. The frequencies of TNFalpha polymorphisms were both similar in patients with mild or severe pancreatitis, so were in pancreatitis patients and in controls. It was suggested that both SNPs of TNFalpha are not genetic risk factor for AP susceptibility (OR 1.63; 95 % confidence interval 1.13 to 4.01 for TNFalpha(-308) and OR 0.86; 95 % confidence interval 0.75 to 1.77 for TNFalpha(-238)) [257].

CFTR

Despite an extensive search, no cause is found for recurrent acute/chronic pancreatitis (idiopathic pancreatitis) in about 20 percent of patients. In these patients, CFTR gene mutations may be identified. The aims of one study were to describe the natural history of pancreatitis associated with the CFTR mutation, to look for genotype-phenotype correlations, and to examine the frequency of CFTR mutations in a population of patients with idiopathic pancreatitis. One hundred consecutive patients with idiopathic pancreatitis were included between 1998 and 2005. Fifty percent had one of the 33 most frequent CFTR gene mutations (common CF mutations, uncommon mutations causing variable phenotypes and variants of unknown significance in 28, 44 and 28 %, respectively). Patients with a CFTR gene mutation were significantly younger than those without (34 vs 40 years). Duration of follow-up (3.5 vs 3 years), proportion of patients with acute pancreatitis as first symptom (76 vs 74 %) were not significantly different. Signs of chronic pancreatitis (ductal changes and pancreatic calcifications), pseudocysts, common bile duct stenosis, exocrine or endocrine insufficiency occurred in 36, 26, 4, 10 and 12 percent of patients with CFTR gene mutations respectively, which was not different from patients without mutations. No phenotype-genotype correlation was observed. The authors concluded that in patients with idiopathic pancreatitis, clinical and radiological manifestations are not related to the presence of a CFTR gene mutation or to the type of mutation [258].

It was assessed whether CFTR gene has a major impact on chronic pancreatitis pathogenesis than that provided by the CFTR mutations. For this aim, it was evaluated clinical parameters, CFTR mutations, and 3 potential regulatory CFTR variants (coding single-nucleotide polymorphisms): c.1540A>G, c.2694T>G, and c.4521G>A. Methods: CFTR gene analysis was performed in a cohort of 136 chronic pancreatitis patients and 93 controls from Spanish population using current scanning techniques (single-strand conformation polymorphism/heteroduplex, denaturing gradient gel electrophoresis, and denaturing high-performance liquid chromatography) and direct sequencing. A higher frequency of CFTR mutations were observed in patients (39 %) than in controls (15 %), differences being mostly attributable to the prevalence of the cystic fibrosis (CF)-causing mutations. The analysis of variants has shown statistically significant differences between patients and controls for c.4521G>A. Furthermore, the multi-marker analysis revealed that the 1540A;2694G;4521A (AGA) haplotype was more prevalent in chronic pancreatitis than controls. Remarkably, this

association was unrelated to CF-causing mutations. It was concluded that the results corroborate the higher susceptibility of CF carriers to chronic pancreatitis and, furthermore, suggest that the AGA haplotype could contribute to an increased risk in the development of chronic pancreatitis irrespective of other CF-causing mutations [259].

SPINK

To study the genetic predisposition, phenotype and prognosis of idiopathic chronic pancreatitis (CP) a prospective observational and case-control study of consecutive patients with CP was performed. Detailed mutational analysis was done for the cationic trypsinogen, SPINK1 and CFTR genes with single-strand conformational polymorphism or restricted fragment length polymorphism, and sequencing. Clinical and disease characteristics of idiopathic versus alcoholic CP, and early onset versus late onset idiopathic CP were compared. Response to multimodality treatment (medical, endoscopic and/or surgical) and prognosis were analysed. Of the 411 patients with CP, 242 had idiopathic etiology (age 28 ± 12 years; 154 men). Malnutrition and cassava were not risk factors. SPINK1 N34S mutation was present in 42 percent of patients with idiopathic CP (vs 4 % controls) and 17 percent of patients with alcoholic CP, which were statistically significant differences. In the CFTR gene, nine patients with idiopathic CP had mutations and 41 patients had polymorphisms (50 % vs 10 % controls). Diabetes developed in 36 percent of patients with idiopathic CP. About 85 percent of patients had significant pain relief with therapy. The probability of surviving for 35 years after onset of idiopathic CP was 83 percent. The typical features of tropical calcific pancreatitis were seen only in 6 percent of patients. It was concluded that strong genetic susceptibility due to SPINK1 and CFTR gene mutations, and comparative phenotype of idiopathic CP in India suggest that the term “tropical calcific pancreatitis” is a misnomer [260].

PRSS3

A sustained imbalance of pancreatic proteases and their inhibitors seems to be important for the development of chronic pancreatitis (CP). Mesotrypsin (PRSS3) can degrade intrapancreatic trypsin inhibitors that protect against CP. Genetic variants that cause higher mesotrypsin activity might increase the risk for CP. It was analyzed all 5 exons and the adjacent non-coding sequences of PRSS3 by direct sequencing of 313 CP patients and 327 controls. Additionally, exon 4 was investigated in 855 patients and 1,294 controls and a c.454+191G>A variant in 855 patients and 1,467 controls. The c.499A>G (p.T167A) variant was analyzed functionally using transiently transfected HEK 293T cells. Results: In the exonic regions, the previously described common c.94_96delGAG (p.E32del) variant and a novel p.T167A non-synonymous alteration were identified. Extended analysis of the p.T167A variant revealed no association to CP and in functional assays p.T167A showed normal secretion and activity. Variants of the intronic regions, including the extensively analyzed c.454+191G>A alteration, were not associated with the disease. Haplotype reconstruction using variants with a minor allele frequency of >1% revealed no CP-associated haplotype. It was concluded that although the trypsin inhibitor-degrading activity qualified PRSS3 as a candidate for a novel CP susceptibility gene, it was not found any association between a specific variant or haplotype and chronic pancreatitis in the cohort with a high suspicion of genetically determined disease [261].

Platelet-derived growth factor

Platelet-derived growth factor (PDGF)-beta is a major signal in proliferation and matrix synthesis through activated pancreatic stellate cells, leading to fibrosis of the pancreas. Recurrent acute pancreatitis (RAP) seems to predispose to chronic pancreatitis (CP) in some patients but not others. It was tested the hypothesis that two known PDGF-beta polymorphisms are associated with progression from RAP to CP. It was also tested the

hypothesis that PDGF-beta polymorphisms in combination with environmental risk factors such as alcohol and smoking are associated with CP. Three hundred eighty-two patients with CP (n=176) and RAP (n=206) and 251 controls were evaluated. Platelet-derived growth factor [beta] polymorphisms +286 A/G (rs#1800818) seen in 5'-UTR and +1135 A/C (rs#1800817) in first intron were genotyped using single-nucleotide polymorphism polymerase chain reaction approach and confirmed by DNA sequencing. Results: The genotypic frequencies for PDGF-beta polymorphisms in positions +286 and +1135 were found to be similar in controls and patients with RAP and CP. There was no difference in genotypic frequencies among RAP, CP, and controls in subjects in the alcohol and smoking subgroups. It was thus concluded that known variations in the PDGF-beta gene do not have a significant effect on promoting or preventing fibrogenesis in pancreatitis [262].

Molecular biology

Glycoprotein 2

Premature activation of pancreatic digestive enzymes is considered as a major factor in the pathogenesis of pancreatitis. Genetic alterations of different pancreatic zymogens or their inhibitors have been associated with chronic pancreatitis. It was sequenced all 12 GP2 exons in 380 German chronic pancreatitis patients and in 182 German control subjects. In addition, we analyzed exon 3 of GP2 in 803 further patients and 1780 controls originating from Germany, the Netherlands, and India by targeted DNA sequencing. It was detected 12 nonsynonymous and 6 synonymous exonic variants. All nonsynonymous changes with exception of c.220C>T (p.R74X) and c.502_503delG (p.G168fsX174) in exon 3 and c.541C>T (p.R181X) in exon 4 were missense mutations and predominantly located in exon 3. All nonsynonymous variants were found in single cases only, with exception of 2 alterations, c.355A>G (p.M119V) and c.409G>A (p. A137T), both located in exon 3. To elucidate the role of these 2 exon 3 variants, we investigated additional patients and controls. The frequency of these variants was similar between patients and controls regardless of ethnic background or cause of chronic pancreatitis. These data suggest that GP2 alterations do not alter the risk for the development of chronic pancreatitis [263].

The aim of one study was to evaluate whether variations in the glycoprotein 2 gene (GP2) may potentially affect the risk of chronic pancreatitis. Six hundred sixty-one French white patients (590 idiopathic chronic pancreatitis, 42 familial chronic pancreatitis, 29 hereditary pancreatitis), 445 Dravidian patients from India (306 tropical calcific pancreatitis, 139 idiopathic chronic pancreatitis), and 962 unrelated healthy subjects (500 French white, 462 Dravidian) participated in this case-control association study. The entire coding sequence of the GP2 gene was searched for conventional genetic variations by direct sequencing, whereas all 12 exons of the GP2 gene were screened for copy number variations by quantitative fluorescent multiplex-polymerase chain reaction. Only 3 rare missense mutations (p.A137T, p.E250D, and p.V432M; only p.E250D was not detected in any control subjects) and 3 common synonymous polymorphisms (c.348C>T, c.714G>C, and c.1275A>G) were identified. The c.348C>T and c.1275A>G variations were found to be contradictorily associated with the disease (ranging from protective effects to disease-predisposing effects) in the French white and Indian populations. It was concluded that the paucity of patient-specific missense mutations and contradictory findings with respect to 2 common polymorphisms in the 2 contrasting populations suggest that the GP2 gene is unlikely to play a major role in the etiology of chronic pancreatitis [264].

T-cell response

Chronic pancreatitis is characterized by alternating phases of acute inflammation and quiescent disease. Involvement of T-cell responses has been suggested, but pancreatitis-specific T cells have not been described. It was characterized T-cell responses against pancreatitis, pancreatic carcinoma-associated antigens, and tetanus toxoid in the bone marrow, blood, and/or pancreatitis lesions of patients with pancreatitis, pancreatic cancer, and healthy individuals. T cells were functionally characterized by antigen-dependent secretion of interferon (IFN)-gamma, interleukin (IL)-4, and IL-10, which indicate type 1, type 2, or regulatory T-cell responses, respectively. Regulatory T cells were characterized by multicolor flow cytometry. Isolated regulatory T cells were tested for their capacity to recognize pancreatitis-associated antigens and to suppress conventional T cells in an antigen-dependent manner. T cell-derived cytokines in tissue lesions were quantified by enzyme-linked immunosorbent assay. Chronic pancreatitis patients showed similar to pancreatic cancer patients and healthy individuals type 1 T-cell responses against tetanus toxoid; however, they exhibited strong IL-10-based T-cell responses against pancreatitis-associated but not pancreatic carcinoma-associated antigens. T cells from pancreatic cancer patients responded to pancreatic cancer-associated but not pancreatitis-associated antigens with IFN-gamma secretion. Pancreatitis-specific IL-10 responses were mediated by IL-10(+)IFN-gamma(-)FoxP3(+) regulatory T cells, which were expanded in the blood, bone marrow, and pancreatitis lesions and possessed the potential to suppress the proliferation of autologous conventional T cells in an antigen-specific manner. Pancreatitis lesions, in comparison with pancreatic carcinomas, contained increased concentrations of IL-10 and reduced levels of IFN-gamma, suggesting pancreatitis-specific activity of regulatory T cells in situ. It was concluded that chronic pancreatitis is associated with disease-specific regulatory T-cell responses [265].

Diagnosics

Numerous publications from academic centers suggest that magnetic resonance cholangiopancreatography (MRCP) can diagnose early chronic pancreatitis and assess pancreatic secretory reserve/function. However, the rigorous composite interpretation methods and quantitative secretory dynamics reported in these studies are not routinely measured in clinical practice. Therefore, the utility of routine MRCP reports in the clinical setting is unknown. Cross-sectional study of patients referred to a tertiary center who underwent both MRCP and endoscopic pancreas function testing (ePFT) for assessment of chronic pancreatitis and abdominal pain. To compare MRCP and sMRCP reports to a reference standard pancreas function test for diagnosis of chronic pancreatitis. Source population: patients seen within a pancreas clinic at a tertiary referral center. MRCP and sMRCP reports were reviewed to record pancreas duct (dilation, side-branch changes), parenchyma enhancement (T_1 , T_2 signal) and physiologic response (duodenal filling, pancreas duct response) to secretin. ePFT was categorized based on previously published data (normal peak bicarbonate >80 mEq/l). Referent values were calculated for MRCP and sMRCP using secretin ePFT as gold standard. A total of 69 patients were identified (mean age 44 ± 12 ; 65 % female). 28 (40 %) patients had abnormal ePFT based on their peak bicarbonate level. The mean bicarbonate values in the abnormal PFT and normal PFT groups were 59 ± 14 and 95 ± 13 mEq/l, respectively. Peak bicarbonate decreased significantly with severity of chronic pancreatitis on MRCP. There was fair agreement of MRCP and ePFT. The pre-stimulation pancreas duct changes reported were found to be the only predictor of abnormal pancreas function. The post-stimulation findings of duodenal filling, T_2 enhancement or change in pancreas duct caliber reported did not improve MRCP agreement with ePFT. Overall diagnostic accuracy, sensitivity and specificity were 70, 85 and 46 percent, respectively, for MRCP reports using ePFT as the gold standard. It was

concluded that pancreas ductal features described on routine MRCP reports correlate with abnormal pancreas function. Current MRCP reports should be standardized to include all radiologic information available in hopes of predicting early chronic pancreatitis [266].

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is well suited for assessment of the pancreas due to its high resolution and the proximity of the transducer to the pancreas, avoiding air in the gut. Evaluation of chronic pancreatitis (CP) was an early target for EUS, initially just for diagnosis but later for therapeutic purposes. The diagnosis of CP is still accomplished using the standard scoring based on nine criteria, all considered to be of equal value. For diagnosis of any CP, at least three or four criteria must be fulfilled, but for diagnosis of severe CP at least six criteria are necessary. The Rosemont classification, more restrictive, aims to standardize the criteria and assigns different values to different features, but requires further validation. EUS-fine needle aspiration (EUS-FNA) is less advisable for diagnosis of diffuse CP due to its potential side effects. Elastography and contrast-enhanced EUS are orientation in differentiating a focal pancreatic mass in a parenchyma with features of CP, but they cannot replace EUS-FNA. The usefulness of EUS-guided celiac block for painful CP is still being debated with regard to the best technique and the indications. EUS-guided drainage of pseudocysts is preferred in non-bulging pseudocysts or in the presence of portal hypertension. EUS-guided drainage of the main pancreatic duct should be reserved for cases in which endoscopic retrograde cholangiopancreatography has failed owing to difficult cannulation of the papilla or difficult endotherapy. It should be performed only by highly skilled endoscopists, due to the high rate of complications [267].

The threshold number of endoscopic ultrasound (EUS) criteria for diagnosing chronic pancreatitis (CP) is variable. The presence of more than three abnormal ductular or parenchymal features is typically used, but the diagnostic significance of fewer EUS criteria is currently unclear. The aim of one study was to determine the prevalence of EUS features of CP in patients without pancreaticobiliary disease and to analyze the association with specific factors of interest. Over a 24-month period, 2,614 patients underwent EUS for an indication unrelated to pancreaticobiliary disease. Main outcome measurements were univariate and multivariate analysis between any EUS abnormality and demographic data and habits. Eighty-two patients (17 %) showed at least one ductular or parenchymal abnormality. Thirty-eight patients presented with only one abnormal feature, 26 patients with two, 12 patients with three, 4 patients with four, and 2 patients with five. Low-level alcohol consumption significantly increased the risk of hyperechoic parenchymal foci, main pancreatic duct (MPD) dilatation and wall hyperechogenicity. Smoking was associated with an increased risk of hyperechoic parenchymal foci. Male gender and advanced age were significantly associated with an increased risk of MPD dilatation. These abnormalities might represent either a clinically silent CP or a toxic effect of smoking and alcohol. Conversely, MPD dilation might represent a normal age-related variant or, alternatively, an effect of chronic low-level alcohol consumption [268].

Function tests

The secretin-pancreozymin test is regarded as the most accurate of the pancreatic exocrine function tests but is cumbersome, time consuming, and invasive because it requires duodenal intubation and hormonal stimulation of the pancreas. Fecal analysis of fat, fecal elastase, or chymotrypsin are more practicable but far less sensitive to detect early stages of pancreatic exocrine insufficiency. Several ¹³C-labeled substrates that are digested by pancreatic enzymes have been proposed for breath tests, thus assessing the intraluminal activity of pancreatic enzymes and therewith the pancreatic exocrine function. Particularly in pediatrics, ¹³C breath tests are suited not only for diagnosis of pancreatic exocrine disorder, but also for therapy control under pancreatic enzyme substitution. However, the costs of

substrates, the high time expenditure, and the lack of standardization still limit the clinical use of these breath tests. This review aims to place into perspective the traditional pancreatic exocrine function tests and the newer ¹³C breath tests [269].

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Secretin endoscopic pancreatic function test

Endoscopic ultrasound (EUS) and hormone-stimulated pancreatic function tests are considered useful, and possibly complementary, in the diagnosis of early chronic pancreatitis (CP). Few past studies have compared either methods with a histological gold standard. The aims were to assess correlations of EUS score and endoscopic pancreatic function test (ePFT) results with the degree of histological fibrosis, as well as the sensitivity of each method for detecting fibrosis. This was a retrospective study of patients who underwent EUS, ePFT, or both within 12 months of pancreatic resection or wedge biopsy. EUS scoring was performed using 9 standard criteria, with ≥ 4 considered abnormal. An ePFT peak bicarbonate concentration < 80 mM was considered abnormal. Surgical specimens were reviewed in a blinded manner by an expert pancreatic pathologist and assigned a fibrosis score from 0 to 12. Correlations of the EUS score and ePFT peak bicarbonate with the fibrosis score are reported using the Spearman correlation coefficient. Sensitivity and specificity was calculated for each method against the histological gold standard (fibrosis score ≥ 2). Twenty-five patients were included. The fibrosis score significantly correlated with the EUS score and the ePFT peak bicarbonate. EUS had a sensitivity of 84 percent (95 % confidence interval 69 to 100 %) and specificity of 100 percent (95 % confidence interval 40 to 100) compared with histology. The ePFT had a sensitivity of 86 percent (95 % confidence interval 67 to 100) and specificity of 67 percent (95 % confidence interval 13 to 100). When both modalities were combined, the sensitivity increased to 100 percent (95 % confidence interval 63 to 100). It was concluded that both EUS and ePFT are useful tests in the diagnosis of CP. Combining EUS with ePFT may improve the sensitivity for detection of early fibrosis [271].

EUS combined with pancreatic function test

Endoscopic ultrasound and endoscopic secretin pancreatic function test may be combined in a single endoscopic session (EUS/ePFT) to diagnose chronic pancreatitis (CP). The primary aim in one study was to assess of the correlation and concordance of combined EUS and secretin ePFT bicarbonate results in suspected minimal change CP. Radial EUS included scoring for nine criteria (normal < 4 criteria) with endoscopic collection of duodenal samples at 15, 30, and 45 min after secretin stimulation (normal peak bicarbonate ≥ 80 mmol/L). Three hundred and two patients completed the EUS/ePFT (252 for suspected minimal change CP, 38 for established CP, 12 for painless steatorrhea). In patients evaluated for suspected minimal change CP, a moderate negative correlation was observed between endoscopic ultrasound score and peak bicarbonate. The EUS and ePFT results were 76 percent concordant and 24 percent discordant. The ePFT was 85 percent sensitive and EUS was 100 percent sensitive for detecting patients with established calcific CP. The EUS/ePFT

diagnosed CP in two of 12 of patients evaluated for painless steatorrhea or diarrhea with weight loss. It was concluded that the combined EUS/ePFT is feasible and safe. There is only moderate correlation and concordance of endoscopic ultrasound and endoscopic pancreatic function test results in patients with suspected minimal change CP. The EUS and endoscopic pancreatic function test results produce complimentary functional and structural information for the evaluation of chronic pancreatitis [272].

PanINs

Chronic pancreatitis (CP) is a predisposing disease for pancreatic carcinoma, however, precise molecular mechanisms of cancer development in the background of CP are ill defined. A total of 443 laser-microdissected pancreatic intraepithelial neoplasias (PanINs), acinar-ductal metaplasia (ADM), and normal ducts from 21 patients with CP were analyzed for loss of heterozygosity (LOH) and immunohistochemical protein expression of p53, p16, and DPC4. Pancreatic intraepithelial neoplasias were analyzed for mutations in p53, p16, and Ki-ras genes by ABI sequencing. Aneuploidy was determined by fluorescence in situ hybridization with probes for chromosomes 3, 7, 8, and 17. Loss of heterozygosity rate in PanIN-1 and ADM was between 2 percent (p53) and 6 percent (p16). In PanIN-3, p53 protein overexpression and loss of expression for p16 and DPC4 protein were seen. Heterozygous mutations of p53 and p16 without LOH were found in PanIN-1A and ADM, whereas homozygous mutations were found in PanIN-3. Aneuploidy increased from PanIN-1A to PanIN-3. Ki-ras mutations were discovered first in PanIN-1. It was concluded that heterozygous mutations of p53 and p16 genes together with chromosomal instability occur early in CP and are clonally expanded, but final inactivation mostly by LOH happens later in pancreatic carcinogenesis. Determination of aneuploidy in pancreatic juice may be of value for early detection and risk assessment in patients with long-standing chronic pancreatitis [273].

Xanthogranulomatous pancreatitis

Xanthogranulomatosis is an idiopathic, rare process in which lipid-laden histiocytes are deposited at various locations in the body. It was present two cases who were treated by duodenum-preserving pancreatic head resection and eventually diagnosed as having xanthogranulomatous pancreatitis. A 30-year-old caucasian man was admitted to our clinic for vague abdominal pain and epigastric dullness. MRCP and endoscopic retrograde pancreatography suggested the existence of chronic pancreatitis. Another 34-year-old caucasian woman was admitted because of right upper quadrant pain. Magnetic resonance cholangiopancreatography demonstrated a dilatation and stone of the main pancreatic duct. Based on a diagnosis of chronic pancreatitis, pancreatic head resection was planned and a laparotomy was performed in both of cases. In both cases, duodenum-preserving pancreatic head resection was performed. Macroscopic and microscopic findings revealed xanthogranulomatous inflammation, which led to a diagnosis of xanthogranulomatous pancreatitis [274].

Alcoholic pancreatitis

Folate plays an essential role in one-carbon metabolism, and a relationship exists between methyl group metabolism and pancreatic exocrine function. Little, however, is known about the mechanism(s) and regulation of folate uptake by pancreatic acinar cells and the effect of chronic alcohol use on the process. It was addressed these issues using the rat-derived pancreatic acinar cell line AR42J and freshly isolated primary rat pancreatic acinar cells as

models. It was found [³H]folic acid uptake to be temperature and pH dependent with a higher uptake at acidic than at neutral/alkaline pH, saturable as a function of substrate concentration at both buffer pH 7.4 and 6.0, inhibited by folate structural analogs and by anion transport inhibitors at both buffer pH 7.4 and 6.0, trans-stimulated by unlabeled folate, adaptively regulated by the prevailing extracellular folate level, and inhibited by modulators of the cAMP/PKA-mediated pathway. Both the reduced folate carrier (RFC) and the proton-coupled folate transporter (PCFT) were found to be expressed in AR42J and in primary pancreatic acinar cells, as well as in native human pancreas with expression of RFC being higher than PCFT. Chronic alcohol feeding of rats (4 weeks; 36 % of calories from ethanol) led to a significant decrease in folate uptake by freshly isolated primary pancreatic acinar cells compared with cells from pair-fed controls; this effect was associated with a parallel decrease in the level of expression of RFC and PCFT. These studies reveal that folate uptake by pancreatic acinar cells is via a regulated carrier-mediated process which may involve RFC and PCFT. In addition, chronic alcohol feeding leads to a marked inhibition in folate uptake by pancreatic acinar cells [275].

Alcohol and genetics

Excessive consumption of alcohol is involved in the onset of pancreatitis. However, most of heavy drinkers do not develop chronic pancreatitis. Various genetic factors appear to be involved in these individual differences in onset of chronic alcoholic pancreatitis. It was therefore investigated a possible association of alcoholic pancreatitis with polymorphisms of the various genes belong to the phase II detoxification enzymes responsible for metabolism of the oxidative compounds, and the several genes that have relevance to inherited pancreatitis. The subjects consisted of 53 patients with chronic alcoholic pancreatitis, 54 alcoholic patients without pancreatic dysfunction, and 42 healthy individuals. DNA was extracted from the peripheral nucleated blood cells of all subjects and genetic mutations and subtypes were analyzed by the PCR and RFLP methods. It was examined the correlation between chronic alcoholic pancreatitis and variants of the phase II detoxification enzymes such as Glutathione S-transferase M1 (GSTM1), glutathione S-transferase theta 1 (GSTT1), NADPH-quinone oxidoreductase 1 (NQO1), and N-acetyl transferase (NAT2). In addition, genes of lipoprotein lipase (LPL), cationic trypsinogen (PRSS1), pancreatic secretory trypsin inhibitor (PSTI), and cystic fibrosis transmembrane conductance regulator (CFTR) were also analyzed. Frequencies of the gene deletion of GSTM1 and GSTT1 in addition to the C-allele frequency of NQO1 tended to be higher in the alcoholic patients with or without pancreatic dysfunction than in the healthy controls although the difference was not significant. The NAT2 gene showed no relation with alcohol. PSTI, LPL, PRSS1, and CFTR genes presented no association with chronic alcoholic pancreatitis. This means that all genes analyzed in the present study lacked association with chronic alcoholic pancreatitis. However, the gene deletion of GSTM1 and GSTT1, and the C-allele of NQO1 cannot be ruled out for association with alcoholism [276].

Correlation to inflammatory bowel disease

Diseases involving the hepatopancreatobiliary (HPB) system are frequently encountered in patients with inflammatory bowel disease (IBD). Hepatobiliary manifestations constitute some of the most common extraintestinal manifestations of IBD. They appear to occur with similar frequency in patients with Crohn's disease or ulcerative colitis. HPB manifestations may occur in following settings:

- disease possibly associated with a shared pathogenetic mechanism with IBD including primary sclerosing cholangitis (PSC), small-duct PSC/pericholangitis and PSC/autoimmune hepatitis overlap, acute and chronic pancreatitis related to IBD

- diseases which parallel structural and physiological changes seen with IBD, including cholelithiasis, portal vein thrombosis, and hepatic abscess
- diseases related to adverse effects associated with treatment of IBD, including drug-induced hepatitis, pancreatitis (purine-based agents), or liver cirrhosis (methotrexate), and reactivation of hepatitis B, and biologic agent-associated hepatosplenic lymphoma

Less common HPB manifestations that have been described in association with IBD include autoimmune pancreatitis (AIP), IgG4-associated cholangitis (IAC), primary biliary cirrhosis (PBC), fatty liver, granulomatous hepatitis, and amyloidosis. PSC is the most significant hepatobiliary manifestation associated with IBD and poses substantial challenges in management requiring a multidisciplinary approach. The natural disease course of PSC may progress to cirrhosis and ultimately require liver transplantation in spite of total proctocolectomy with ileal-pouch anal anastomosis. The association between AIP, IAC, and elevated serum IgG4 in patients with PSC is intriguing. The recently reported association between IAC and IBD may open the door to investigate these complex disorders. Further studies are warranted to help understand the pathogenesis of HPB manifestations associated with IBD, which would help clinicians better manage these patients. An interdisciplinary approach, involving gastroenterologists, hepatologists, and, in advanced cases, general, colorectal, and transplant surgeons is advocated [277].

Pancreatic diabetes

In one study, it was determined the incidence and pathology of pancreatic diabetes in Japan. It was examined the epidemiology of pancreatic diabetes in Japan in 2005 by using a nationwide stratified random-sampling method. Especially, it was focused on newly developed diabetes in association with the occurrence of pancreatic disease (true pancreatic diabetes). A total of 19,500 individuals received treatment for true pancreatic diabetes, accounting for 0.8 percent of patients with diabetes. Prevalence was estimated to be 15.2 per 100,000 with an annual onset incidence of 1.1 per 100,000. With regard to the complications in true pancreatic diabetes, the incidence of retinopathy was lower than that in types 1 and 2 diabetes. Among true pancreatic diabetes with chronic pancreatitis, alcoholic pancreatitis was found in the largest sector. Furthermore, as many as 54 percent were continuous drinkers, and 67 percent received insulin therapy. The frequency of hypoglycemia was high in regular drinkers treated with insulin. Hypoglycemia was a major cause of death in patients who were on insulin and continuous drinkers [278].

Intestinal transit time

Gastrointestinal transit was assessed, in 40 male outpatients with alcohol-related chronic pancreatitis and 18 controls, by scintigraphy after a liquid meal labeled with ^{99m}Tc-technetium-phytate. Blood and urinary glucose, fecal fat excretion, nutritional status, and cardiovascular autonomic function were determined in all patients. The influence of diabetes mellitus, malabsorption, malnutrition, and autonomic neuropathy on abnormal gastrointestinal transit was assessed by univariate analysis and Bayesian multiple regression analysis. Accelerated gastrointestinal transit was found in 11 patients who showed abnormally rapid arrival of the meal marker to the cecum. Univariate and Bayesian analysis showed that diabetes mellitus and autonomic neuropathy had significant influences on rapid transit, which was not associated with either malabsorption or malnutrition. In conclusion, rapid gastrointestinal transit in patients with alcohol-related chronic pancreatitis is related to diabetes mellitus and autonomic neuropathy [279].

Glucagon-like peptide-2

Glucagon-like peptide-2 (GLP-2) is a nutrient-released gastrointestinal (GI) hormone that acts as an intestinal growth factor, and exogenous GLP-2 has been shown to increase superior mesenteric artery (SMA) blood flow. It was aimed to investigate how assimilation of nutrients affects postprandial GLP-2 responses and to correlate these with postprandial SMA blood flow. Responses of the GI hormone glucose-dependent insulintropic polypeptide (GIP) and GLP-2 were measured following an 80-min liquid meal test in 8 patients (6 males) with chronic pancreatitis (CP) and pancreatic exocrine insufficiency (PEI) and 8 healthy control subjects (5 males). Postprandial GI hormone responses were correlated with change in SMA flow as assessed by the resistance index. Patients with CP and PEI exhibited the greatest postprandial GLP-2 responses. No difference was observed with regard to GIP. GLP-2, but not GIP, responses correlated significantly with postprandial SMA flow. These results suggest that delayed assimilation of nutrients in patients with CP and PEI increases the secretion of GLP-2 – possibly due to delivery of a larger nutrient load to the distal part of the small intestine, where GLP-2 secreting L-cells are abundant – and that this hypersecretion of GLP-2 is associated with a higher SMA flow [280].

Treatment options

In patients suffering from chronic pancreatitis, pain as the predominant symptom remains a therapeutic challenge which often cannot be tackled conservatively. Since pancreatic duct obstruction – frequently within the pancreatic head – is an important etiological factor, treatment in these cases aims at decompressing the duct either endoscopically or surgically. Endoscopic drainage includes sphincterotomy, dilation of strictures, removal of stones, and insertion of a stent; it has a success rate of 30-100 percent. Surgical treatment may be accomplished by drainage or resection procedures. Drainage procedures (such as the longitudinal opening of the pancreatic duct followed by a pancreaticojejunostomy) can be performed with a low rate of postoperative complications (6-30 %) and mortality (0-2 %), and can achieve long-term pain relief in 65-85 percent of the cases. Furthermore, there are a variety of resection procedures such as pancreaticoduodenectomy (Whipple procedure), pylorus-preserving pancreaticoduodenectomy, different types of the duodenum-preserving pancreatic head resection (i.e. Beger, Frey, or Büchler procedures), segmentectomy, and V-shaped excision of the pancreatic duct. However, the surgical procedure of choice is controversially discussed. While it has been shown that parenchyma-preserving surgery is superior to more extensive resections, it remains unclear which of the modifications of the parenchyma-sparing procedures is suited best for which case. Recently, two randomized controlled trials have demonstrated that surgical treatment is superior to endotherapy in long-term pain reduction, physical health score results, and the number of reinterventions. Thus, in patients with chronic pancreatitis refractory to conservative medical treatment, surgery rather than endotherapy is the standard of care. Parenchyma-preserving resections should preferably be performed because they ensure lower morbidity and mortality, preserve endocrine function, and improve quality of life [281].

Chronic pancreatitis is a common disorder of which the underlying pathogenic mechanisms still are incompletely understood. In the last decade, increasing evidence has shown that activated pancreatic stellate cells play a key role in the fibrosis development associated with chronic pancreatitis as well as pancreatic cancer. During pancreatic injury or inflammation, quiescent stellate cells undergo a phenotypic transformation, characterized by smooth muscle alpha-actin expression and increased synthesis of extracellular matrix proteins. Hitherto, specific therapies to prevent or reverse pancreatic fibrosis are unavailable. A review addressed current insights into pathological mechanisms underlying chronic pancreatitis and their applicability as concerns the development of potential future therapeutic approaches [282].

Surgery, overview

To establish the current status of surgical therapy for chronic pancreatitis, recent published reports were examined in the context of the historical advances in the field. The basis for decompression (drainage), denervation, and resection strategies for the treatment of pain caused by chronic pancreatitis was reviewed. These divergent approaches have finally coalesced as the head of the pancreas has become apparent as the nidus of chronic inflammation. Local resection of the pancreatic head, with or without duct drainage, and duodenum-preserving pancreatic head resection offer outcomes as effective as pancreaticoduodenectomy, with lowered morbidity and mortality. Local resection or excavation of the pancreatic head offers the advantage of lowest cost and morbidity and early prevention of postoperative diabetes. The late incidences of recurrent pain, diabetes, and exocrine insufficiency are equivalent for all 3 surgical approaches. It was concluded that local resection of the pancreatic head appears to offer best outcomes and lowest risk for the management of the pain of chronic pancreatitis [283].

The Beger operation

Central pancreatectomy is indicated for treatment of traumatic lesions and benign or low-grade tumors of the pancreatic neck and proximal body. After central pancreatectomy, the proximal pancreatic stump is usually closed, and pancreaticojejunostomy or pancreaticogastrostomy carried out with the distal pancreas. Adopting these reconstructive techniques in most series revealed a prevalence of postoperative fistula that was higher than after pancreaticoduodenectomy or left pancreatectomy. It was presented a case treated by novel application of the reconstructive method of the Beger procedure. Reconstruction by Roux-en-Y double pancreaticojejunostomy after central pancreatectomy was done in a 71-year-old female suffering from insulinoma of the proximal pancreatic body. Postoperative complications were not observed. No alteration of pancreatic endocrine and exocrine function occurred at 22-month follow-up. Therefore, double pancreaticojejunostomy is a promising method for treating the proximal pancreatic stump after central pancreatectomy [284].

Modified Beger's operation

Chronic pancreatitis, a benign, inflammatory process, can cause enlargement of the pancreatic head, which is accompanied by severe pain and weight loss and often leads to a significant reduction in the quality of life (QoL). The clinical experience relates to the results attained with duodenum and organ-preserving pancreatic head resection in 160 patients during a 10-year period. The QoL is assessed during the follow-up period by using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire. Two reoperations were required in consequence of anastomosis bleeding and small bowel obstruction, but no mortality was noted in the postoperative period. The duration of hospitalization ranged between 7 and 12 days. The mean follow-up time was 5 years (range 1-10 years). The late mortality rate was 6.9 percent. The QoL improved in 89 percent of the cases. One hundred thirty-three of the patients became complaint-free, whereas 16 displayed moderate symptoms, and the weight increased by a median of 13 kg (range, 4-30 kg). The postoperative endocrine functions remained in almost the same stage as preoperatively. It was concluded that this 10-year experience clearly demonstrates that this duodenum and organ-preserving pancreatic head resection technique is a safe and effective procedure, which should be preferred in the surgical treatment of the complications of chronic pancreatitis [285].

Frey's procedure

Few studies have addressed long-term pain relief after Frey's procedure (local head resection with lateral pancreaticojejunostomy, LR-LPJ) for chronic pancreatitis. One retrospective study evaluated pain control using a validated score and risk factors associated with failure to achieve complete pain relief following LR-LPJ. Sixty of 134 patients with chronic pancreatitis underwent LR-LPJ and were evaluated prospectively using the Izbicki pain score before surgery, and 1, 2, 5 and 7 years later. Analysis was on an intention-to-treat basis and predictors of complete pain relief were identified by multivariable analysis. After a median follow-up of 6.4 years, the median pain score was reduced from 46 to 10, which was a significant difference, with partial or complete pain relief in 75 percent of patients, and a significant reduction in median number of episodes requiring hospitalization (from 4 to 0). Preoperative use of opiate medication (odds ratio (OR) 30), continuous pattern of pain (OR 23) and occurrence of postoperative complications (OR 11) were significant predictors of failure to achieve complete pain relief after surgery. It was concluded that Frey's procedure leads to significant and sustained long-term pain relief in patients with chronic pancreatitis. Patients should be referred for surgery before opiates are needed to relieve pain [286].

Transduodenal sphincterotomy

Transduodenal sphincterotomy (TS) has fallen into disuse since endoscopists developed techniques to treat sphincter problems nonsurgically. However, some patients experience recurrent sphincter strictures after endoscopic sphincterotomy (ES), with the ampulla endoscopically inaccessible, and pancreas divisum (PD); these patients are referred to a surgeon because they are unsuitable for ES. The medical records of patients who underwent transduodenal sphincterotomy between 1997 and 2005 were reviewed. A total of 82 patients, including 47 women and 35 men with a mean age of 47 years (range, 26-67 years), underwent TS. Previous unsuccessful endoscopic retrograde cholangiography and ES were the indications for TS in 44 patients, and previous gastric surgery with duodenal bypass was the indication for TS in 21 patients. Five patients underwent TS because of a PD and 10 because of the intraoperative findings of daughter hydatid cysts in the common bile duct and of a wide communication between the cyst cavity and the intrahepatic biliary tree. Two patients were referred to our institution after a surgical papillotomy performed elsewhere. Symptoms included abdominal pain in 100 percent of patients, nausea and/or vomiting in 78 percent of patients, and referred back pain in 56 percent of patients. Acute pancreatitis was present in the history of 26 patients, including 23 with previous ES. All patients underwent TS. Sphincteroplasty of the accessory papilla was performed in all patients with PD. Cornerstones of a successful TS are depicted. Asymptomatic hyperamylasemia was observed in 37 patients, and cholangitis and pancreatitis, which was resolved with conservative management, occurred in two patients. One patient developed an intra-abdominal abscess that was treated with image-guided percutaneous drainage. No perioperative deaths occurred in this series. The mean length of follow-up evaluation was 84 months (range, 16-115 months). Good results were achieved in 53 patients (74 %), fair results in 17 patients (24 %), and poor results in 2 patients (3 %). Both patients with poor results required reoperation because of recurrent pancreatitis and pancreatic pseudocyst. It was concluded that transduodenal sphincterotomy still represents, although undoubtedly with updated indications compared with the past, a surgical procedure that must be up to date, ensuring absolutely satisfactory results [287].

Islet cell autotransplantation

For patients with severe chronic pancreatitis, total or completion pancreatectomy with islet cell autotransplantation (IAT) can alleviate pain and avoid the complications of diabetes. Several genetic mutations, specifically, PRSS1, CFTR, and SPINK1, are associated with chronic pancreatitis. Few reports have focused on the benefit of this operation for this subset of patients. Between 2000 and 2009, 118 patients were treated with total pancreatectomy and IAT for chronic pancreatitis. Patients with known genetic mutations were then selected for further analysis. Of the 118 patients, 16 (14 %) patients were identified as having genetic mutations, including CFTR (n=10), PRSS1 (n=4), and SPINK1 (n=2) mutations. Mean patient age was 31 years (range, 15-59) with an equal male-to-female ratio (50:50). Preoperatively, patients required an average of 185 ± 60 morphine equivalents (MEQ) (median, 123 MEQ) for preoperative pain control. No patients were taking insulin before operation. After resection with IAT, patients were discharged from the hospital with a daily average of 22 ± 4 units of insulin with 6 (38 %) patients requiring fewer than 15 units of insulin at the time of discharge. At a mean follow-up of 22 months, mean insulin requirements decreased significantly to 15 U/day. A total of 7 (44 %) patients required 15 or fewer units daily, and 4 (25 %) patients were completely insulin-independent. Average daily narcotic usage at most recent follow-up decreased to 70 MEQ (median, 0) with 10 (63 %) patients currently narcotic-independent. Analyses of the 36-item short-form health survey and the McGill Pain Questionnaire demonstrated a significant improvement in quality-of-life parameters and pain assessment. It was concluded that in patients who suffer from genetically linked chronic pancreatitis, pancreatic resection with IAT should be considered as an early therapeutic option to decrease chronic abdominal pain while preserving endogenous endocrine function [288].

To clarify the implication of pancreatic findings on transabdominal ultrasound and/or abdominal computed tomographic scan on outcomes of islet isolation and endocrine function after total pancreatectomy (TP) with islet autotransplantation (IAT). It was made a retrospective review of islet isolations and graft functions in a cohort of patients with chronic pancreatitis who received TP with IAT from 2007 to 2009. Patients were categorized into 2 groups on the basis of their transabdominal ultrasound or computed tomographic findings before IAT: early group (normal or equivocal of Cambridge classification) and advanced group (mild to marked). A total of 12 patients (early group, n = 6; advanced group, n=6) were included. Total islet yield per pancreas weight and per patient body weight in the early group was significantly higher compared with that in the advanced group (6989 ± 659 vs 3567 ± 615 islet equivalents per gram). Four patients (67 %) in the early group became insulin-free, whereas 2 patients (33 %) in the advanced group obtained insulin independence. However, both groups maintained islet graft function and similar glycated hemoglobin levels after transplantation. It was concluded that excellent glycemic control was observed in both groups of patients who received total pancreatectomy with islet autotransplantation, although the early group showed a significantly better outcome of islet isolation [289].

The probability of insulin independence after intraportal islet autotransplantation (IAT) for chronic pancreatitis treated by total pancreatectomy (TP) relates to the number of islets isolated from the excised pancreas. The goal of one study was to correlate the islet yield with the histopathologic findings and the clinical parameters in pediatric (age, <19 years) chronic pancreatitis patients undergoing TP-IAT. Eighteen pediatric chronic pancreatitis patients aged 5 to 18 years (median, 16 years) who underwent TP-IAT were studied. Demographics and clinical history came from medical records. Histopathologic specimens from the pancreas were evaluated for presence and severity of fibrosis, acinar cell atrophy, inflammation, and nesidioblastosis by a surgical pathologist blinded to clinical information. Fibrosis and acinar atrophy significantly negatively correlated with islet yield, particularly in hereditary chronic pancreatitis. Previous duct drainage surgeries also had a strong negative correlation. Islet yield was better in younger (preteen) children and in those with pancreatitis

of shorter duration. It was concluded that for preserving beta cell mass, it is best to perform TP-IAT early in the course of chronic pancreatitis in children, and prior drainage procedures should be avoided to maximize the number of islets available, especially in hereditary disease [290].

ESWL

Obstructive pancreatic duct stones can cause recurrent attacks of acute pancreatitis and chronic abdominal pain. Use of extracorporeal shock wave lithotripsy (ESWL) for treatment of abdominal pain associated with obstructive pancreatic duct stones has been well documented. However, its effect on prevention of recurrent pancreatitis in this group of patients has not been studied. Patients with recurrent episodes of acute pancreatitis due to obstructive pancreatic duct stones not amenable to endoscopic removal were therefore prospectively examined. All patients underwent ESWL by a pancreatologist using an electromagnetic shock wave lithotripter. After ESWL, the patients were followed up for recurrence of acute pancreatitis. Ten patients underwent 13 sessions of ESWL. Complete and partial ductal clearances were achieved in 7 and 3 patients, respectively. The mean length of follow-up was 20 months (range, 12-36 months). Three patients had recurrent attacks of acute pancreatitis during the follow-up period, caused by recurrence of obstructive stones in two and presence of main duct stricture in one patient. It was concluded that extracorporeal shock wave lithotripsy of obstructive pancreatic duct stones in patients with recurrent attacks of acute pancreatitis can prevent further attacks. New episodes of acute pancreatitis in this group of patients may indicate stone recurrence or presence of strictures [291].

Pancreatic-pleural fistula

Pancreatic-pleural fistula is an uncommon complication of chronic pancreatitis occurring as a result of disruption of the main pancreatic duct and tracking of pancreatic fluid through the retroperitoneum into one or both thoracic cavities. The optimal treatment strategy for pancreatic-pleural fistula has traditionally been medical management followed by operative therapy for patients who fail to respond to conservative treatment. Review of the literature revealed 63 adult patients with pancreatic-pleural fistula published in English between 1970 and 2008. The majority of patients were male (71 %) and there was a predominance of alcohol-associated chronic pancreatitis (51 %). There were 10 complications (16 %) and 2 deaths (3 %) reported. Most patients were treated initially with medical therapy (87 %). Medical therapy was deemed to have failed after an average period of 35 ± 5 days. Total duration of therapy for patients in whom operative intervention was required after attempted medical management was 40 ± 6 days, which was greater than the surgery alone cohort. In total, operative treatment was successful more often than medical therapy (94 % vs 31 %). Analysis from this series thus indicates that a majority of patients recover from pancreatic-pleural fistula without sequelae (81 %). Attempts at prolonged periods of medical therapy tend to delay the resolution of the fistula compared with patients who undergo definitive operative intervention early in the course of treatment [292].

Pancreatic enzyme therapy

In chronic pancreatitis over a course of years to decades, pancreatic parenchyma is gradually lost and pain is gradually decreasing as signs and symptoms of malabsorption appear. Appearance of calcifications is a late sign and in many cases coincides with appearance of steatorrhea. Decreasing output of insulin and glucagon results in diabetes

mellitus, which is characterized by a high risk of hypoglycemia (brittle diabetes). In most instances, measurement of fecal concentration of elastase may be sufficient to diagnose exocrine pancreatic insufficiency. Fecal fat analysis is useful to establish malabsorption and to monitor pancreatic enzyme replacement therapy. Components essential to the optimal management of chronic pancreatitis are control of pain, improvement of maldigestion, management of diabetes and of complications like cysts or strictures, and alcohol and nicotine abstinence. Patients with pain are evaluated for structural abnormalities which can be treated endoscopically or surgically. Conservative treatment of pain includes fat-reduced diet, nonnarcotic analgesics, alcohol and smoking cessation, and, if not successful, an 8-week trial of high-dose pancreatic enzymes. Pancreatic enzymes are used for the treatment of maldigestion. Digestion of fat is the determining factor in pancreatic insufficiency. Treatment success is defined clinically by improved body weight and consistency of feces. Modern pancreatin preparations are engineered as acid-resistant, pH-sensitive microspheres. Using such preparations, most patients will reduce their steatorrhea to <15 g fat per day during supplementation of 25,000-40,000 IU of lipase per meal, but in selected cases larger doses may be needed, depending on size of the meal and severity of the disease. Efficacy of enzyme replacement therapy is influenced by denaturation of lipase by gastric acid, improper timing of enzymes, coexisting small-intestinal mucosal disease, rapid intestinal transit and effects of diabetes. One review focused on pathophysiology, diagnosis and treatment of pancreatic steatorrhea [293].

Pancreatic-enzyme replacement therapy (PERT) is the standard of care to prevent maldigestion, malnutrition, and excessive weight loss in patients with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP) or pancreatic surgery (PS). The objective of one study was to assess the efficacy and safety of a new formulation of pancrelipase (pancreatin) delayed-release 12,000-lipase unit capsules (CREON) in patients with EPI due to CP or PS. This was a double-blind, randomized, multicountry, placebo-controlled, parallel-group trial enrolling patients ≥ 18 years old with confirmed EPI due to CP or PS conducted in clinical research centers or hospitals. After a 5-day placebo run-in period (baseline), patients were randomized to pancrelipase (72,000 lipase units per meal; 36,000 per snack) or placebo for 7 days. All patients received an individually designed diet to provide at least 100 g of fat per day. The primary efficacy measure was the change in coefficient of fat absorption (CFA) from baseline to end of the double-blind period, analyzed using non-parametric analysis of covariance. Secondary outcomes included the coefficient of nitrogen absorption (CNA), clinical symptoms, and safety parameters. In total, 25 patients (median age of 54 years, 76 % male) received pancrelipase and 29 patients (median age of 50 years, 69 % male) received placebo. The mean \pm SD change from baseline in CFA was significantly greater with pancrelipase versus placebo: 32 ± 19 % versus 9 ± 13 percent. Similarly, the mean \pm SD change from baseline in CNA was significantly greater for pancrelipase versus placebo: 98 ± 82 percent versus 24 ± 101 percent. Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were observed with pancrelipase versus placebo. Treatment-emergent adverse events (TEAEs) were reported in five patients (20.0%) in the pancrelipase group and in six (20.7%) in the placebo group; the most common were gastrointestinal (GI) events and metabolism/nutrition disorders. There were no treatment discontinuations due to TEAEs. Pancrelipase delayed-release 12,000 lipase unit capsules were effective in treating fat and nitrogen maldigestion with a TEAE rate similar to that of placebo in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery [294].

One study was conducted to compare the efficacy of a new formulation of pancrelipase (pancreatin) delayed-release 12,000-lipase unit capsules with placebo in children with EPI due to CF. It was a multicenter, randomized, double-blind, placebo-controlled, 2-period crossover, superiority study of the new formulation of pancrelipase delayed-release 12,000-lipase unit capsules in children aged 7 to 11 years with CF and EPI. In each period, pancrelipase or identical placebo capsules were taken for 5 days. The primary outcome

measure was the coefficient of fat absorption (CFA); secondary outcome measures were the coefficient of nitrogen absorption (CNA) and clinical symptoms. The latter were assessed based on patient-reported daily stool frequency, stool consistency (hard, formed/normal, soft, or watery), flatulence (none, mild, moderate, or severe), and abdominal pain (none, mild, moderate, or severe). Safety measures included vital signs, physical examinations, standard laboratory safety tests (hematology and biochemistry), and adverse events. Seventeen patients were randomized to treatment and 16 completed the study; 1 patient withdrew consent during the first treatment period and was not included in the efficacy analysis. Patients' median age was 8 years (range, 7-11 years); 12 patients (71 %) were male. CFA values were significantly greater for pancrelipase compared with placebo, with least squares mean values of 83 ± 2.7 percent and 47 ± 3 percent, respectively. The results were similar for CNA, with mean values of 80 ± 3 percent and 45 ± 3 percent, a significant difference. Pancrelipase treatment had significantly greater effects on CFA and CNA in patients with a placebo CFA < 50 percent than in those with a placebo CFA >50 percent (both parameters significant difference). Significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily stool frequency were observed with pancrelipase compared with placebo. Symptoms of EPI were less severe and remained relatively stable during pancrelipase treatment, but worsened slightly during receipt of placebo. Treatment-emergent adverse events were reported in 5 patients (29 %) during receipt of pancrelipase and in 9 patients (56 %) during receipt of placebo; these were predominantly gastrointestinal events. There were no discontinuations due to treatment-emergent adverse events and no serious adverse events. In this study in children with EPI due to CF, the new formulation of pancrelipase delayed-release capsules was associated with improvements in CFA, CNA, stool properties, and EPI symptoms compared with placebo. Pancrelipase delayed-release capsules appeared to be well tolerated [295].

Pain

Chronic visceral pain is frequent, extremely debilitating, and generally resistant to pharmacological treatment. It has been shown that chronic visceral inflammation, through altered afferent visceral sensory input, leads to plastic changes in the central nervous system that ultimately sustain pain. Therefore approaches aiming at modulation of brain activity are attractive candidates to control visceral pain. It was reported findings of a phase II, sham-controlled clinical trial assessing the clinical effects and brain metabolic correlates of a 10-day course of daily sessions of slow-frequency, repetitive transcranial magnetic stimulation (rTMS) targeting the right secondary somatosensory cortex (SII) in patients with chronic pancreatitis and severe visceral pain. The results show a significant reduction in pain after real rTMS that lasted for at least 3 weeks following treatment. These clinical changes were correlated with increases in glutamate and N-acetyl aspartate (NAA) levels – neurometabolites associated with cortical activity and brain damage – as measured by in vivo single-voxel proton magnetic resonance spectroscopy (1H-MRS). Adverse effects in the real rTMS group were mild and short-lasting. The results support preliminary findings showing that modulation of right SII with rTMS is associated with a significant analgesic effect and that this effect is correlated with an increase in excitatory neurotransmitter levels such as glutamate and NAA [296].

Octreotide LAR®

Octreotide long acting repeatable (LAR) is commonly used to control the symptoms of patients with functional neuroendocrine tumors. Unfortunately, most patients escape control over time and require higher LAR doses or more frequent rescue therapy to remain asymptomatic. Previous work has shown that body weight and monthly LAR dose will

significantly affect circulating plasma octreotide levels in patients undergoing therapy. To determine if other parameters change circulating plasma octreotide levels, it was prospectively studied 82 patients undergoing long-term LAR therapy. Multivariate analysis demonstrated that the plasma octreotide levels decrease by approximately 3.4 percent for each unit of body mass index (BMI) increase, adjusting for sex and monthly LAR dose. Plasma octreotide levels for females were approximately 48 percent higher than those for males, adjusting for BMI and monthly LAR dose. Initial and subsequent octreotide LAR doses should take into consideration sex and BMI. Males are estimated to require 14 mg higher monthly LAR doses than females with the same BMI [297].

Octreotide and its long acting form Octreotide LAR are widely used to control the symptoms of patients with functional neuroendocrine tumors. Unfortunately, most patients escape control over time and require higher LAR doses or more frequent rescue therapy to remain asymptomatic. Previous work has shown that body weight and monthly LAR dose will significantly affect circulating plasma octreotide levels in patient undergoing therapy. To determine the parameters that change circulating plasma octreotide levels it was prospectively studied 82 (43 F/39M) patients undergoing long term LAR therapy. Multivariate analysis demonstrated that the plasma octreotide level decreases by approximately 3.4 percent for each unit that the BMI increases, adjusting for gender and monthly LAR dose. Similarly, plasma octreotide levels for females were about 47.6 percent higher than males, adjusting for BMI and monthly LAR dose. It was concluded that initial and subsequent octreotide LAR doses should take into consideration gender and BMI. Males are estimated to require 14.1 mg (SD 7.25) higher monthly LAR dose than females with the same BMI. Also the monthly LAR dose should be increased by 1.3 mg (SD 0.62) for each unit of BMI increase to achieve the same plasma octreotide level [298].

Gluteal injection of octreotide

Gluteal intramuscular injection remains an important method for delivery of a variety of medications including octreotide LAR. In one study, only 32 percent of gluteal injections were delivered into the intramuscular space [Chan et al, Eur J Radiol, 2006]. It was examined nursing factors that are associated with successful gluteal intramuscular injections. Patients receiving intramuscular injection of octreotide LAR at were identified. Pelvic CTs were reviewed for evaluation of injection success, measurement of injection depth, and skin to muscle depth. Twenty-two nurses were interviewed. 251 intended intramuscular injections between 2008 were evaluable by CT. 105 (42 %) were associated with subcutaneous nodules indicating subcutaneous placement; 146 (58 %) were deemed successful intramuscular injection. Factors associated with successful intramuscular injection included self-reported indicators of experience, landmark based localization of injection site, depth of needle insertion, and use of non-syringe hand. It was concluded that a significant number of octreotide LAR injections are not successfully delivered into the intramuscular space. Nursing experience and injection technique were highly associated with successful injection. Nursing education may improve successful intramuscular injection rate [299].

Gluteal intramuscular injection of octreotide LAR is effective for control of carcinoid syndrome and delay of tumor growth in midgut carcinoid tumors. However, many intended gluteal intramuscular injections are delivered subcutaneously which may lead to altered pharmacokinetics and suboptimal therapeutic outcomes. It was examined gender related issues in gluteal intramuscular injections. Patients receiving intramuscular injection of octreotide LAR were identified. Pelvic CTs were reviewed for evaluation of injection success, measurement of injection depth, and skin to muscle depth. 251 intended intramuscular injections were evaluable by CT. Among these, 119 (47 %) were given to males; 132 (53 %) were given to females. 105 (42 %) were associated with subcutaneous nodules indicating subcutaneous placement; 146 (58 %) were deemed successful intramuscular injection. Successful intramuscular injection rate was significantly lower in females (42 % vs 77%).

Females had lower BMI (mean, 26.6 vs 28.8), but greater skin to muscle depth at optimal injection site (mean, 34 vs 24 mm). BMI correlated linearly with skin to muscle depth. Among those with failed intramuscular injections, depth of needle placement was deeper among females (mean, 30 vs 25 mm). Self reported nursing experience level affected success rate of gluteal intramuscular to a greater degree among females compared to males. It was concluded that gluteal intramuscular injections are more difficult in females due to greater skin to muscle distance despite lower BMI. Increased nursing education and introduction of longer needles are needed [300].

Gluteal intramuscular injection remains an important method for delivery of a variety of medications including octreotide LAR. 251 intended intramuscular injections were evaluated. 105 (42 %) were associated with subcutaneous nodules (mean size 19 mm) indicating subcutaneous placement; 146 (58 %) were deemed successful intramuscular injection. CT assessed reasons for missed injections include insufficient needle penetration (36 %), injection site being too cranial (36 %), lateral (11 %), caudal (9 %), and insufficient needle length (10 %). Among missed injections, mean distances are: skin to injection deposit, 29 (12-57) mm; injection deposit to muscle, 15 (1-94) mm; skin to tissue sciatic nerve plane, 72 (43-103) mm. Among all injections, the mean distance from skin to muscle at optimal injection site and from skin to sciatic nerve plane is 29 (9-63) mm, and 58 (38-108) mm respectively. Percentage of all patients with skin to muscle depth at optimal injection site \leq 33 mm, and \leq 38 mm are 66 percentage, and 86 percent, respectively. Successful, intramuscular injection rate is higher among patient with skin to muscle depth at optimal injection site \leq 38 mm (64 % vs 21 %). It was concluded that common reasons for unsuccessful intramuscular injection are poor injection site selection, and not advancing needle to full length. In 14 to 34 percent of patients, needles greater than 38 mm (length of needle available in US) would be needed for successful intramuscular injection [301].

Quality of life

In chronic pancreatitis wellbeing is considerably impaired, but the different factors affecting quality of life (QoL), have not been identified yet. Sixty-nine patients with chronic pancreatitis were evaluated (M/F 55/14; mean age 47 ± 10 years). Different degrees of pancreatic damage were defined using the Cambridge classification; pain intensity and frequency were assessed using pain index. QoL was measured using EORTC QLQ-C30 and the PAN26 questionnaire. Although developed for pancreatic cancer, the C30/PAN26 has been validated for chronic pancreatitis. Digestive symptoms, financial difficulties, fear of future health and general pain scales showed considerable effects of chronic pancreatitis on QoL. It was observed significant negative correlation between mean QoL scores and pain index in almost all domains. Pain intensity affects QoL scales more often than pain frequency. BMI correlated positively with QoL in global health status, altered bowel habits, body image and satisfaction with health care domains. It was concluded that Pain index, BMI, Cambridge classification and disease duration are the most important factors adversely affecting QoL in chronic pancreatitis [302].

Surgery for chronic pancreatitis is indicated for intractable pain or the treatment of complications. This retrospective cohort study evaluated the applicability of pain coping and quality-of-life (QOL) scoring in patients with chronic pancreatitis. Between 1995 and 2008, 155 patients underwent surgery for chronic pancreatitis in two Dutch university hospitals. Medical charts were reviewed, and QOL and coping with pain were assessed by two validated questionnaires. Median follow-up was 6 years. The etiology was alcohol related in 48 percent. Some 111 resections and 46 drainage procedures were performed. Fifty-seven patients had major complications and the hospital mortality rate was 1.3 percent. After surgery the number of patients needing analgesics was significantly reduced. Alcohol

consumption significantly reduced pain coping mechanisms. Overall, QOL remained poor after surgery. Scores on three dimensions of the QOL questionnaire were significantly better after drainage than after resection procedures. The authors concluded that in general, QOL after surgery for chronic pancreatitis remains poor, owing to pre-existing lifestyle and comorbidity. Patients selected for a pancreatic duct drainage procedure have a better postoperative QOL than those undergoing resectional procedures. Alcohol consumption is associated with poor ability to cope with pain after surgery and should be discouraged [303].

Experimental

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain in chronic pancreatitis. One study aimed to investigate the effect of NSAIDs on the inflammation and fibrosis progression in trinitrobenzene sulfonic acid-induced chronic pancreatitis in rats. Chronic pancreatitis was induced by trinitrobenzene sulfonic acid infusion into rat pancreatic ducts. Naproxen treatment (20 and 40 mg/kg per os and intraperitoneally) started two weeks after the induction of chronic pancreatitis for 3 weeks. Histological analysis of the pancreas, Van Gieson staining, and contents of hydroxyproline were used to evaluate pancreatic damage and fibrosis. Furthermore, the effect of naproxen on nociceptive reflective behaviors and serum tumor necrosis factor-alpha concentration were studied, and immunohistochemical analysis of alpha-smooth muscle actin in the pancreas was performed. Pancreatic collagen content and alpha-smooth muscle actin expression were significantly higher in the chronic pancreatitis group treated with high-dose (40 mg/kg per oral) naproxen. High-dose naproxen administered orally significantly aggravated pancreatic fibrosis and inflammation. Instead of playing an analgesic role, high-dose naproxen decreased the thermal withdrawal latencies in chronic pancreatitis in rats [304].

Pancreatic stellate cells

In chronic pancreatitis, pancreatic stellate cells (PSCs) play a central role in tissue fibrogenesis. Transforming growth factor beta₁ (TGF-beta₁) and the Th2 lymphokines such as interleukin (IL)-13 are major profibrogenic cytokines in many organs. Activated PSCs produce various inflammatory cytokines including TGF-beta₁. In this study, it was investigated whether IL-13 affects pancreatic fibrogenesis by modulating the functions of PSCs. IL-13 promoted PSCs proliferation without activation through the suppression of autocrine TGF-beta₁. IL-13 enhanced Stat6 phosphorylation in PSCs but Stat6 was not involved in the suppression of TGF-beta₁. IL-13 inhibited the transcriptional activity of NF-kappaB, and the expression of mutant I-kappaB reproduced the suppression of autocrine TGF-beta₁ and promoted PSCs proliferation. Taken together, we demonstrated that IL-13 promotes PSCs proliferation through the suppression of the transcriptional activity of NF-kappaB, resulting in the decrease of autocrine TGF-beta₁. This finding provides an unequivocal evidence of IL-13 participation in pancreatic fibrosis, illustrating a new strategy for chronic pancreatitis [305].

Pancreatic stellate cells (PSCs) play a pivotal role in pancreatic inflammation and fibrosis. In the pancreas, in addition to oxidative metabolism, ethanol can be metabolized by esterification with fatty acids to form fatty acid ethyl esters such as palmitic acid ethyl ester (PAEE). It was examined the effects of ethanol (at 20 or 50 mM), acetaldehyde (at 200 microM), or PAEE (at 100 microM), on PSCs functions. PSCs did not express mRNAs for pancreatic triglyceride lipase and carboxyl ester lipase. Ethanol and acetaldehyde, but not PAEE, induced production of procollagen type I C-peptide. Ethanol, but not acetaldehyde or PAEE, induced interleukin-8 production. PAEE activated activator protein-1, but not nuclear factor kappaB. In addition, PAEE activated extracellular signal-regulated kinase, c-Jun N-

terminal kinase, and p38 mitogen-activated protein kinase. Specific activation of signal transduction pathways and cell functions by ethanol and its metabolites may play a role in alcohol-induced pancreatic injury [306].

Interleukin 33 (IL33) is a cytokine belonging to the IL1 family and it binds to a complex of the ST2L/IL1 receptor accessory protein (IL1RAcP). To define the role of IL33 in fibrogenesis of the pancreas, the expression of IL33, ST2L and IL1RAcP was examined in chronic pancreatitis tissues. The effects of IL33 on the functions of human pancreatic myofibroblasts were also investigated. Tissue samples were obtained surgically. The expression of IL33, ST2L and IL1RAcP was evaluated by standard immunohistochemical procedures. Messenger RNA expression for IL33, ST2L and IL1RAcP was analysed by northern blotting and real-time PCR analyses, and protein expression was assessed by western blotting and ELISA. Cell proliferation and migration were assessed by a ³H-thymidine incorporation assay and the modified Boyden chamber assay, respectively. IL33, ST2L and IL1RAcP were expressed by alpha-SMA-positive myofibroblasts in the fibrosis of chronic pancreatitis. In human pancreatic myofibroblasts, IL33 was weakly immunoreacted without any stimuli, and this was markedly enhanced by IL1beta, tumour necrosis factor alpha (TNF-alpha) and lipopolysaccharide (LPS) via the mitogen-activated protein kinase (MAPK)-dependent AP-1 activation pathway. ST2L mRNA was weakly detected in unstimulated cells, and IL4 and interferon gamma (IFN-gamma) strongly enhanced ST2L expression via STAT6 and STAT1 signalling, respectively. IL33 rapidly induced the phosphorylation of MAPKs and Ikbeta, and enhanced the expression of inflammatory mediators (IL6, IL8, IP-10, Gro-alpha, Gro-beta and MCP-1) in IL4- or IFNgamma-pretreated cells. IL33 stimulated the proliferation and migration of pancreatic myofibroblasts. It was concluded that IL33 and its receptor complex (ST2L and IL1RAcP) constitute a novel signalling system which may play an important role in the pathogenesis of chronic pancreatitis [307].

The gastrointestinal hormone cholecystokinin (CCK) can induce acute pancreatitis in rodents through its action on acinar cells. Treatment with CCK, in combination with other agents, represents the most commonly used model to induce experimental chronic pancreatitis. Pancreatic stellate cells (PSC) are responsible for pancreatic fibrosis and therefore play a predominant role in the genesis of chronic pancreatitis. However, it is not known whether PSC express CCK-receptors. Using real-time PCR techniques, it was now demonstrated that CCK1- and CCK2-receptors are expressed on rat PSC. Interestingly both CCK and gastrin significantly induced type I collagen synthesis. Moreover, both inhibit proliferation. These effects are comparable to TGF-beta- stimulated PSC. Furthermore, the natural agonists CCK and gastrin induce activation of pro-fibrogenic pathways Akt, ERK and Src. Using specific CCK1- and CCK2-receptor inhibitors, it was found that Akt activation is mainly mediated by CCK2R. Akt activation by CCK and gastrin could be inhibited by PI3K inhibitor wortmannin. Activation of ERK and downstream target Elk-1 could be inhibited by MEK-inhibitor U0126. These data suggest that CCK and gastrin have a direct activating effect on PSC, are able to induce collagen synthesis in these cells and therefore appear to be important regulators of pancreatic fibrogenesis. Furthermore, similar to TGF-beta both CCK and gastrin inhibit proliferation in PSC [308].

Experimental

It has previously been reported the finding that pancreatic stellate cells (PSCs) have a phagocytic function. The aim of one study was to investigate whether engulfment of gram-positive bacteria by PSCs plays any role in the pathogenesis of pancreatic fibrosis. Rat PSCs were cultured with lipoteichoic acid (LTA) or bacteria and analyzed for alpha-smooth muscle actin expression and collagen secretion. Human pancreata were obtained from routine autopsies of 20 cases; a diagnosis of gram-positive sepsis was made in 10 of the cases (sepsis group), but sepsis had not been diagnosed in the other 10 cases (control group). Pancreatic tissue was stained with anti-LTA antibody, and the severity of pancreatic fibrosis

was evaluated by histological scoring. Bacteria and LTA were internalized into the cytoplasm of cultured PSCs. Exposure to LTA or bacteria significantly increased alpha-smooth muscle actin expression and collagen secretion. Blockade of toll-like receptor 2 significantly inhibited the increase in collagen secretion in response to LTA. There was no significant difference in the severity of pancreatic fibrosis between the sepsis group and the control group. It was concluded that the fibrogenic action of PSCs seems to be more strongly associated with activation of the toll-like receptor-dependent pathway than it is with phagocytosis of bacteria by PSCs [309].

AUTOIMMUNE PANCREATITIS

The Honolulu Consensus Document

Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by swelling of the pancreas, narrowing of the main pancreatic duct, elevation of serum immunoglobulin G or G4 level or presence of several autoantibodies, or lymphoplasmacytic infiltration and fibrosis in the pancreas. Autoimmune pancreatitis has been extensively reported from Japan, Europe, and the United States. Whereas the descriptions of AIP from Japan have predominantly been based on the presence of a distinct clinical phenotype, reports from Europe and the United States describe at least 2 histopathologic patterns in patients' condition currently diagnosed as AIP, viz, lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct centric pancreatitis (IDCP) or granulocyte epithelial lesion (GEL)-positive pancreatitis. Although the 2 entities share common histopathologic features (periductal lymphoplasmacytic infiltration and peculiar periductal fibrosis), expert pathologists can accurately distinguish them based on other unique histopathologic features. Clinically, the 2 entities have similar clinical presentation (obstructive jaundice/pancreatic mass and a dramatic response to steroids) but differ significantly in their demography, serological characteristics, other organ involvement, and disease relapse. While LPSP is associated with elevation in titers of nonspecific autoantibodies and serum IgG4 levels, IDCP does not have definitive serological autoimmune markers. All experts agreed that the clinical phenotypes associated with LPSP and IDCP should be nosologically distinguished; however, their terminology was debated. Whereas most experts agreed that the entities should be referred to as type 1 and type 2 AIP, respectively, others had concerns regarding use of the term "autoimmune" to describe IDCP [310].

Other diagnostic criteria

The aim of one study was to clarify the problems of the Japanese criteria for autoimmune pancreatitis (AIP) in comparison with the other criteria. It was retrospectively investigated the clinical, imaging, serological, and histopathologic features, together with other organ involvement and response to steroid, in 50 patients with AIP diagnosed on the basis of the Japanese, Korean, HISORt, and Asian criteria. Thirty-five patients with pancreatic cancer were enrolled as a control group. Forty (80 %) of 50 patients received a diagnosis of AIP on the basis of the Japanese criteria. Imaging findings and serological parameters fulfilled the Japanese criteria in 40 (80 %) and 50 (100 %) of the patients. Pathological findings fulfilled the Japanese criteria in 6 (43 %) of 14 patients. All of the 10 patients who did not have a diagnosis of AIP did not fulfill the imaging criteria. Serological parameters fulfilled the Japanese criteria in 8 (23 %) of 35 patients with pancreatic cancer. The sensitivities of the Japanese, Korean, HISORt, and Asian criteria for AIP were 80 percent, 86 percent, 92 percent, and 82 percent, respectively. The specificities of those 4 criteria were 89 percent, 89 percent, 97 percent, and 89 percent, respectively. The authors concluded that the low sensitivity of imaging criteria and low specificity of serological criteria were a problems in the Japanese criteria [311].

Pathophysiology of IgG

The patients with autoimmune pancreatitis usually present with jaundice and a pancreatic head mass, presumed to have pancreatic cancer, and they often undergo pancreatic resection. Elevated serum IgG4 levels (>135 mg/dL) help to distinguish autoimmune pancreatitis from pancreatic cancer. However, when the biopsy from a pancreatic mass

shows dense chronic inflammation and fibrosis and the serum IgG4 level is not available, it presents a diagnostic dilemma whether it represents autoimmune pancreatitis or peritumoral pancreatitis. It was performed IgG4 immunohistochemistry on 25 cases of autoimmune pancreatitis-lymphoplasmacytic sclerosing pancreatitis, 7 cases of autoimmune pancreatitis with granulocytic epithelial lesions, 8 cases of nonspecific pancreatitis, 15 cases of pancreatitis associated with pancreatic ductal adenocarcinoma, and 5 biopsies of pancreatic adenocarcinoma with variable inflammation. The distribution of IgG4-positive cells was noted in each case. Eighty-four percent (21/25) of autoimmune pancreatitis-LPSP cases showed diffuse and dense staining for IgG4, with more than 50 positive plasma cells per high-power field (range, 50-150 cells/hpf) in the highest density area. Most (5/7) cases of autoimmune pancreatitis-granulocytic epithelial lesions were negative for IgG4. Thirty-nine percent of nonspecific pancreatitis and peritumoral pancreatitis cases stained positive for IgG4, but the distribution was focal and none of the cases showed more than 50 IgG4-positive cells/hpf in the highest density area of IgG4 staining. IgG4-positive cells in peritumoral pancreatitis and nonspecific pancreatitis cases were closely associated with malignant glands and areas of acute inflammation in some cases. Using a cutoff of 50 IgG4-positive cells/hpf, the sensitivity of IgG4 staining for classical autoimmune pancreatitis-LPSP versus other types of pancreatitis was 84 percent, the specificity was 100 percent. Hence, it could be concluded that diffuse and dense staining (>50 positive cells/hpf) for IgG4 is specifically seen in autoimmune pancreatitis-LPSP, and IgG4 staining along with the histologic features and serum IgG4 levels may be very helpful in diagnosing autoimmune pancreatitis [312].

High levels of IgG₄-positive plasma cells are commonly seen in autoimmune pancreatitis. It has become evident that autoimmune pancreatitis is one component of a larger multi-system disease. IgG₄-positive plasma cells have been identified in many extrapancreatic tissues, including the colon, biliary tract, liver, and lungs, and thus the term "IgG₄-related sclerosing disease" has been proposed. Awareness of IgG₄-related sclerosing disease is important, as it has been shown to mimic other conditions like malignancy. One review discussed IgG₄-related colitis and its potential for mimicking inflammatory bowel disease [313].

IgG4-related systemic disease is a recently described entity with protean manifestations. It was describe a patient who developed inflammation and fibrosis in multiple organs over 20 years, sequentially involving his pancreas, bile ducts, gallbladder, submandibular and lacrimal glands, and kidneys. He had an elevated serum IgG4 level. Retrospective analysis of biopsies showed strongly positive tissue immunostaining for IgG4, confirming the diagnosis of IgG4-related systemic disease. This case illustrates the natural history of partially treated IgG4-related systemic disease and its varied clinical presentations. Early diagnosis and treatment is important, as the condition is highly steroid-responsive [314].

IgG4-related disease has been identified in various organs, but whether or not there are organ-specific characteristics related to the etiologic factors is still unknown. Here, it was carried out a cross-sectional study of 114 patients with IgG4-related disease. On the basis of the location of the lesions, the patients were classified into 5 groups: head and neck (n=23), thoracic (n=16), hepatic and pancreatobiliary (n=27), retroperitoneal (n=13), and systemic (n=35). All groups had similar clinicopathologic features in various aspects. However, there were some organ-specific features: for example, the proportion of the female patients was significantly higher in the head and neck group, serum IgG4 concentrations were significantly higher in the head/neck and systemic groups, and all kidney lesions were associated with extrarenal disease. Unique pathologic features were dense fibrosis in dacryoadenitis, numerous lymph follicles in sialadenitis and dacryoadenitis, and obliterative arteritis in lung lesions. In addition, an epithelioid granuloma and rheumatoid nodule were noted within IgG4-related lesions in 2 patients, 1 each with a history of tuberculosis and rheumatoid arthritis, respectively. Malignant tumors (2 lung cancers and 1 malignant lymphoma) were identified after the diagnosis of IgG4-related disease in 3 patients, all in the systemic group. In conclusion, this study showed organ-specific features of IgG4-related disease. Further study

is necessary to conclude whether these features reflect different manifestations of a single disease entity or suggest different underlying etiologic factors [315].

Autoimmune pancreatitis (AIP) is recognized as a distinct clinical entity, identified as a chronic inflammatory process of the pancreas in which the autoimmune mechanism is involved. Clinically and histologically, AIP has two subsets: type 1 – lymphoplasmatic sclerosing pancreatitis with abundant infiltration of the pancreas and other affected organs with immunoglobulin G4-positive plasma cells, and type 2 – duct centric fibrosis, characterized by granulocyte epithelial lesions in the pancreas without systemic involvement. In the diagnosis of AIP, two diagnostic criteria are used – the HISORt criteria and Asian Diagnostic Criteria. In the differential diagnosis, the pancreatic cancer must be excluded by endosonographically guided pancreatic biopsy. Typical signs of AIP are concomitant disorders in other organs (kidney, liver, biliary tract, salivary glands, colon, retroperitoneum, prostate). Novel clinicopathological entity was proposed as an “IgG4-related sclerosing disease” (IgG4-RSC). Extensive IgG4-positive plasma cells and T lymphocyte infiltration is a common characteristics of this disease. Recently, IgG4-RSC syndrome was extended to a new entity, characterized by IgG4 hypergammaglobulinemia and IgG4-positive plasma cell infiltration, this being considered an expression of a lymphoproliferative disease, “IgG4-positive multiorgan lymphoproliferative syndrome”. This syndrome includes Mikulicz's disease, mediastinal fibrosis, autoimmune hypophysitis, and inflammatory pseudotumor in lung, liver, and breast. In the therapy of AIP, steroids constitute first-choice treatment. High response to the corticosteroid therapy is an important diagnostic criterion. In the literature, there are no case-control studies that determine if AIP predisposes to pancreatic cancer [316].

An elevated serum titer of immunoglobulin G4 (IgG4), the least common (3 % to 6 %) of the 4 subclasses of IgG, is a surrogate marker for the recently characterized IgG4-related sclerosing disease. The syndrome affects predominantly middle-aged and elderly patients, with male predominance. The patients present with symptoms referable to the involvement of one or more sites, usually in the form of mass lesions. The prototype is IgG4-related sclerosing pancreatitis (also known as autoimmune pancreatitis), most commonly presenting as painless obstructive jaundice with or without a pancreatic mass. Other common sites of involvement are the hepatobiliary tract, salivary gland, orbit, and lymph node, but practically any organ-site can be affected, such as retroperitoneum, aorta, mediastinum, soft tissue, skin, central nervous system, breast, kidney, prostate, upper aerodigestive tract, and lung. The patients usually have a good general condition, with no fever or constitutional symptoms. Common laboratory findings include raised serum globulin, IgG, IgG4, and IgE, whereas lactate dehydrogenase is usually not raised. Some patients have low titers of autoantibodies (such as antinuclear antibodies and rheumatoid factor). The disease often shows excellent response to steroid therapy. The natural history is characterized by the development of multiple sites of involvement with time, sometimes after many years. However, the disease can remain localized to 1 site in occasional patients. The main pathologic findings in various extranodal sites include lymphoplasmacytic infiltration, lymphoid follicle formation, sclerosis and obliterative phlebitis, accompanied by atrophy and loss of the specialized structures of the involved tissue (such as secretory acini in pancreas, salivary gland, or lacrimal gland). The relative predominance of the lymphoplasmacytic and sclerotic components results in 3 histologic patterns: pseudolymphomatous, mixed, and sclerosing. Immunostaining shows increased IgG4+ cells in the involved tissues (>50 per high-power field, with IgG4/IgG ratio >40%). The lymph nodes show multicentric Castleman disease-like features, reactive follicular hyperplasia, interfollicular expansion, or progressive transformation of germinal centers, with the unifying feature being an increase in IgG4+ plasma cells on immunostaining. The nature and pathogenesis of IgG4-related sclerosing disease are still elusive. Occasionally, the disease can be complicated by the development of malignant lymphoma and possibly carcinoma [317].

Type 1 and type 2

The term "AIP" appears to encompass at least two distinct subtypes, type 1 and type 2. Type 1 AIP is the pancreatic manifestation of a systemic fibroinflammatory disease called immunoglobulin G4-associated systemic disease. Type 2 AIP affects younger patients, does not have a gender predilection and is associated with normal serum immunoglobulin G4 levels. Existing criteria are geared toward diagnosis of type 1; type 2 AIP can be definitively diagnosed only on pancreatic histology. Both subtypes respond to corticosteroid therapy. However, there are no standardized protocols for initial treatment or management and prevention of relapses in AIP. A novel antibody for AIP has recently been identified and its performance needs validation from other centers. Newly published strategies for differentiating AIP from pancreatic cancer are available. Much needs to be elucidated with regard to its cause, pathogenesis, treatment of relapse and long-term outcomes. A multidisciplinary team, familiar with the disease, is critical in making the correct diagnosis [318].

Autoimmune pancreatitis (AIP) has been divided into subtypes 1 (lymphoplasmacytic sclerosing pancreatitis) and 2 (idiopathic duct centric pancreatitis). It was compared clinical profiles and long-term outcomes of types 1 and 2 AIP by comparing clinical presentation, relapse, and vital status of 78 patients with type 1 AIP who met the original HISORT criteria and 19 patients with histologically confirmed type 2 AIP. The ages were 62 ± 14 versus 48 ± 19 years which was a significant difference and the patients had a significantly greater prevalence of increased serum levels of immunoglobulin G4 (47/59, 80 %, vs 1/6, 17 %). Patients with type 1 were significantly more likely than those with type 2 to have proximal biliary, retroperitoneal, renal, or salivary disease (60 % vs 0 %). Inflammatory bowel disease was associated with types 1 and 2 (6 % vs 16 %). During median clinical follow-up periods of 42 and 29 months, respectively, 47 percent of patients with type 1 and none of those with type 2 experienced a relapse. In type 1 AIP, proximal biliary involvement (hazard ratio [HR], 2.12) and diffuse pancreatic swelling (HR, 2.00) were predictive of relapse, whereas pancreaticoduodenectomy significantly reduced the relapse rate (vs the corticosteroid-treated group; HR, 0.15). After median follow-up periods of 58 and 89 months (types 1 and 2, respectively), the 5-year survival rates for both groups were similar to those of the age- and sex-matched US population. It was concluded that types 1 and 2 AIP have distinct clinical profiles. Patients with type 1 AIP have a high relapse rate, but patients with type 2 AIP do not experience relapse. However, autoimmune pancreatitis does not affect long-term survival [319].

IgG-negative cases

Autoimmune pancreatitis (AIP) is considered to be a pancreatic lesion of IgG4-related systemic disease, but about 20 percent of AIP patients do not have elevated serum IgG4 levels. One study aimed to clarify the pathophysiology of AIP patients without elevated serum IgG4 levels. Fifty-eight AIP patients were divided into two groups: those with elevated serum IgG4 levels (>135 mg/dL; S-IgG4-positive AIP) and those without (S-IgG4-negative AIP). The 2 groups' clinical, serological, radiological, and histological findings, as well as salivary and lacrimal gland function, were compared. Serum IgG4 levels were elevated in 45 AIP patients and normal in 13 patients. In S-IgG4-negative AIP patients, the female ratio tended to be high; obstructive jaundice was less likely; abdominal pain and acute pancreatitis were more likely; segmental swelling of the pancreatic body and/or tail was more common; sclerosing extrapancreatic lesions, salivary and lacrimal gland dysfunction, and abundant infiltration of IgG4-positive plasma cells in the gastric mucosa were less likely; and conservative follow-up was sometimes implemented. Histological examination of the pancreas of S-IgG4-negative

AIP showed lymphoplasmacytic sclerosing pancreatitis (LPSP) rather confined to the pancreas (n=4), inadequate material (n=2), and pancreatic fibrosis showing infiltration of lymphocytes without infiltration of IgG4-positive cells or neutrophils (n=2). It was concluded that clinicopathological features of S-IgG4-negative AIP differed from those of S-IgG4-positive AIP. Some S-IgG4-negative AIP cases are LPSP rather confined to the pancreas. S-IgG4-negative AIP may include idiopathic duct-centric pancreatitis (IDCP) or sclerosing pancreatitis other than LPSP or IDCP [320].

AIP-related diabetes

In autoimmune pancreatitis, mechanism(s) of paradoxical glycemic control improvement (GCI) often occurring after pancreatic resection and steroid therapy are not fully elucidated. Using image quantitation, AIP cases (n=10) with pre- and post-surgical glucose values were compared with chronic pancreatitis (CP) and normal pancreas (NP) regarding percent chromogranin immunohistochemistry (IHC) positivity as a surrogate marker of endocrine endowment; intra-islet T and B lymphocyte and plasma cell enumeration with CD3, CD20, and IgG4 IHC; and CD34 IHC islet vascularity quantitation. Postsurgical GCI, noted in 8/10 (80 %) AIP cases, approached statistical significance compared to CP. Endocrine endowment reduction, noted by a lower percent of chromogranin + pancreatic parenchyma, was seen in AIP (4.5 %) and CP (3.2 %) compared to NP (8.0 %); only the CP decrease was statistically significant since AIP often had ductular endocrine neogenesis. Regression suggested an inverse correlation between endocrine endowment and GCI in AIP. AIP islets were smaller and disrupted by inflammatory cell infiltration. Compared to CP, AIP islets had higher CD3 + and CD20 + cell densities. IgG4 + plasma cells were often present at a high density in AIP but typically preserved the islets. Intra-islet CD34 staining showed a lower average vascularity in AIP compared to NP. The study reaffirms postsurgical GCI in AIP. Prominent intra-islet inflammation and decreased vascularity in AIP may contribute to diabetogenic effects. Endocrine cell neogenesis and relative islet preservation despite islet inflammatory infiltration may explain the paradoxical GCI in AIP [321].

AIP-related gastritis

Autoimmune pancreatitis is in some patients associated with other inflammatory diseases. In one study, it was aimed to elucidate the pathologic characteristics of AIP-associated gastritis (AIP-G). It was evaluated and compared the pathologic findings and immunohistochemical expressions of immunoglobulin G (IgG)4 and IgG in gastric biopsy specimens from 13 AIP-G patients with those from patients of 2 control groups. It was divided the AIP-G patients who did not receive steroid therapy into two groups: without *Helicobacter pylori* (HP) infection and with HP infection. The control groups comprised 19 patients who were diagnosed with chronic active gastritis associated with HP infection and 7 patients with nonsteroidal anti-inflammatory drug-induced gastritis. It was classified the findings for the gastric mucosa into those for the upper and the lower lamina propria. The characteristic finding of AIP-G groups was diffusely lymphoplasmacytic infiltration in the lamina propria. The IgG4-positive plasma cell/IgG-positive plasma cell ratios (IgG4/IgG ratios) in both the upper and lower lamina propria in the AIP groups without steroid therapy were predominantly higher than the corresponding values in the other groups. In the steroid-negative groups, the IgG4/IgG ratio in the lower lamina propria was predominantly higher than that in the upper lamina propria, irrespective of the HP status. In conclusion, diffuse lymphoplasmacytic infiltration in the lamina propria and increased IgG4/IgG ratio in the gastric mucosa (notably in the lower lamina propria) may be the characteristic findings of AIP-associated gastritis [322].

AIP-related hypothyroidism

It was reported the association between AIP and hypothyroidism and discussed whether hypothyroidism in AIP is another manifestation of IgG4 systemic disease or a true association. In a large cohort of patients with AIP (n=97) meeting HISORt criteria it was studied the association between AIP and hypothyroidism defined by the clinical use of thyroxine replacement therapy. For comparison, it was used age- and sex-matched healthy controls (n=100) randomly selected from a group of healthy individuals presenting between 1999 and 2001. The AIP group was similar to the control group in age and sex distribution, respectively. Clinical hypothyroidism requiring thyroxine supplementation was observed in 14 patients with AIP (14 %) versus in 4 patients in the control group (4 %), which was a statistically significant difference. Patients with AIP with hypothyroidism were older than patients with AIP without hypothyroidism. There was no difference in sex distribution among patients with AIP with and without hypothyroidism. The prevalence of hypothyroidism was similar in the IgG4-seropositive and -seronegative patients. Similarly, the prevalence of hypothyroidism was similar in those with (n=47) and without (n=50) other organ involvement defined as the presence of proximal bile duct stricture, retroperitoneal fibrosis, tubulointerstitial nephritis, or extensive lymphadenopathy. The prevalence of hypothyroidism (overt and subclinical) in the general population was reported as 4.6 percent in the National Health and Nutrition Examination Survey III. Multiple studies in the past have described a multifocal fibrosclerosing disease involving sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, retro-orbital fibrosis, and Riedel thyroiditis [323].

AIP-related sclerosing cholangitis

IgG4-related sclerosing cholangitis (IgG4-SC) is one of several diseases associated with autoimmune pancreatitis (AIP). However, diffuse cholangraphic abnormalities seen in association with AIP may resemble those seen in primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma. IgG4-SC responds well to steroid therapy, whereas in contrast, liver transplantation is the only effective therapy for PSC, and surgical intervention is also needed for cholangiocarcinoma. The aim of one review was to establish the diagnostic procedures for IgG4-SC. A literature search was conducted, covering English-language articles dealing with IgG4-SC published between 1991 and 2010. As clinical data on IgG4-SC are limited, the author also took into consideration his own clinical experience with the treatment of IgG4-SC over a period of more than 19 years. When intrapancreatic stenosis is detected, pancreatic cancer should be ruled out. If multiple intrahepatic stenosis is evident, PSC should be discriminated on the basis of cholangiographic findings and liver biopsy with IgG4 immunostaining. An association with inflammatory bowel disease (IBD) is suggestive of PSC. If stenosis is demonstrated in the hepatic hilar region, cholangiocarcinoma should be discriminated by US, EUS, IDUS, and bile duct biopsy. For diagnosis of IgG4-SC, coexistence of AIP is the most useful finding. However, the most important consideration for clinicians is to be aware of IgG4-SC when encountering patients with obstructive jaundice [324].

MRCP versus ERCP

The aim of one study was to determine the role of magnetic resonance cholangiopancreatography (MRCP) for diagnosing autoimmune pancreatitis (AIP) and the accuracy of MRCP in depicting the main pancreatic duct (MPD) morphology of AIP using endoscopic retrograde cholangiopancreatography (ERCP) as the reference standard. Thirty-eight AIP patients, 40 pancreatic cancer patients, and 40 patients with normal pancreas were included. MRCP was interpreted in association with cross-sectional magnetic resonance

images regarding MPD morphology, pancreatic parenchyma, and extrapancreatic abnormalities. Main pancreatic duct was interpreted as narrowed when a narrowed-appearing segment on MRCP was associated with upstream dilatation or pancreatic parenchymal abnormalities in the same location. Accuracy of MRCP for depicting MPD morphology of AIP (65 %) was significantly lower than those for pancreatic cancer (89 %) or normal pancreas (100 %). The inaccuracy in AIP was primarily (10/12) due to overestimation of MPD narrowing. Of various differing MRCP findings between AIP and pancreatic cancer, multiple MPD narrowing (AIP vs cancer, 27/38 vs 0/40) and upstream MPD dilatation greater than 5 mm in diameter (AIP vs cancer, 0/38 vs 10/40) could exclude pancreatic cancer and AIP, respectively. It was concluded that MRCP cannot replace ERCP for the diagnostic evaluation of AIP but may deserve to be used when ERCP has been unsuccessful or is difficult to perform [325].

Endoscopic ultrasonographic pattern

The classical appearance of autoimmune pancreatitis in abdominal imaging is diffuse pancreatic enlargement, but the focal form appears as a mass and often involves the pancreatic head; this scenario represents a challenging diagnostic problem because these features also resemble pancreatic cancer. It was presented the endoscopic ultrasound findings of seven patients with autoimmune pancreatitis in order to highlight the ambiguous features and the features pivotal for the diagnosis [326].

Differential diagnosis

A Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society have presented Japanese consensus guidelines for management of autoimmune pancreatitis regarding differential diagnosis in extrapancreatic lesions [327].

Eosinophilia

In autoimmune pancreatitis (AIP), the prevalence, interrelationships, and significance of peripheral eosinophilia, allergic disorders, and eosinophil infiltration in the pancreas remain unclear. From medical records, it was obtained data on peripheral eosinophil counts at presentation and follow-up, and clinical diagnoses of allergic disorders in 97 AIP patients (78 type 1 and 19 type 2), which were compared with matched healthy controls. Available pancreatic histologic specimens were graded for eosinophils. Peripheral eosinophilia was defined as counts $>0.5 \times 10^9$ per liter. Among 78 type 1 AIP patients (mean age 62 ± 14 years, 77 % men), peripheral eosinophilia at presentation was diagnosed in 12 percent and allergic disorders in 15 percent (vs 0 and 4% in controls, respectively). Allergic disorders were observed in 27 and 11 percent of type 1 AIP with and without eosinophilia, respectively. Patients with and without peripheral eosinophilia were similar in clinical profile. Moderate-to-severe eosinophil infiltration was present in 67 percent of pancreas resection specimens and did not correlate with peripheral eosinophilia. Type 2 AIP did not differ from type 1 AIP in any of these parameters. It was concluded that peripheral eosinophilia, allergic disorders, and pancreatic eosinophil infiltration are associated with AIP. Eosinophilia in autoimmune pancreatitis may not reflect an allergic phenomenon, but appears to be consistent with autoimmune mechanism [328].

Serum leptin

Serum leptin and adiponectin determinations have been proposed as markers for distinguishing pancreatic cancer and chronic pancreatitis from autoimmune pancreatitis; however, no studies exist in patients with autoimmune pancreatitis and in those with intraductal papillary mucinous tumors of the pancreas. The aim of one paper was to evaluate the circulating concentrations of receptor for advanced glycation end products (RAGE), leptin and adiponectin in patients with chronic pancreatic diseases. Seventy-five consecutive patients with chronic pancreatic diseases (47 males, 28 females; mean age 67 years; range 37-97 years) were studied: six (8 %) had autoimmune pancreatitis, 23 (31 %) had chronic pancreatitis, 34 (45 %) had pancreatic cancer and the remaining 12 (16 %) had intraductal papillary mucinous tumors of the pancreas. Leptin, adiponectin and RAGE were determined in serum using commercially available kits. The leptin concentrations were normalized to the lower and upper reference limits because of the different gender reference ranges. Normalized leptin concentrations were significantly lower in chronic pancreatitis patients and in those with pancreatic cancer compared to the overall population, whereas autoimmune pancreatitis patients had significantly higher concentrations of this protein compared to the overall population. RAGE and adiponectin concentrations were similar among the four groups of patients studied. Among the clinical variables considered, only pain was significantly related to leptin concentrations. It was suggested that serum leptin is a good serum marker for differentiating autoimmune pancreatitis patients from those with chronic pancreatitis and pancreatic cancer [329].

Immunoglobulins

Until now, there was no international consensus on the diagnostic criteria for autoimmune pancreatitis (AIP). As for serologic criteria, the HISORt criteria use elevated immunoglobulin (Ig) G4 alone, whereas the Asian diagnostic criteria include elevations of total IgG or IgG4, or the presence of autoantibodies. One study was mainly aimed at determining whether the combined measurement of total IgG and IgG4 could increase the diagnostic sensitivity for AIP while maintaining specificity, compared with IgG4 alone. Another aim was to determine the utility of autoantibodies to diagnose AIP. It was prospectively measured total serum IgG and IgG4 together in 82 consecutive patients with AIP, and seropositivity was defined as elevation of either total IgG or IgG4. To evaluate specificity in the differentiation of AIP from pancreatic cancer, total serum IgG and IgG4 were prospectively measured in 110 patients with pancreatic cancer. Also, the detection rates of antinuclear antibody (ANA) and rheumatoid factor (RF) were retrospectively reviewed in patients with AIP. In patients with AIP, the sensitivity of IgG4 (≥ 135 mg/dL) was 53 percent (43/82), significantly higher than that (46 %, 38/82) of total IgG ($\geq 1,800$ mg/dL). The sensitivity of combined measurement of total IgG and IgG4 for AIP was 68 percent (56/82), significantly higher than that of IgG4 alone. The specificity of total IgG and IgG4 in the differentiation of AIP from pancreatic cancer was 96 and 99 %, respectively. The specificity of combined measurement of total IgG and IgG4 was 96 percent, but it was not significantly different from that of IgG4 alone. The sensitivity of ANA ($\geq 1:80$) and RF was 24 percent (19/78) and 20 percent (13/64), respectively. All but one patient who had positive results for ANA or RF also showed elevations of either total IgG or IgG4, respectively. The authors concluded that the combined measurement of total serum IgG and IgG4 may increase diagnostic sensitivity without sacrificing specificity, compared with IgG4 alone. However, the measurement of ANA or RF may show no additional benefit when combined with total serum IgG and IgG4 [330].

Autoantibodies

Autoimmune pancreatitis is thought to be an immune-mediated inflammatory process, directed against the epithelial components of the pancreas. The objective of one study was to identify novel markers of disease and to unravel the pathogenesis of AIP. To explore key targets of the inflammatory process, it was analyzed the expression of proteins at the RNA and protein level using genomics and proteomics, immunohistochemistry, western blot, and immunoassay. An animal model of AIP with LP-BM5 murine leukemia virus-infected mice was studied in parallel. RNA microarrays of pancreatic tissue from 12 patients with AIP were compared with those of 8 patients with non-AIP chronic pancreatitis. Expression profiling showed 272 upregulated genes, including those encoding for immunoglobulins, chemokines and their receptors, and 86 downregulated genes, including those for pancreatic proteases such as three trypsinogen isoforms. Protein profiling showed that the expression of trypsinogens and other pancreatic enzymes was greatly reduced. Immunohistochemistry showed a near-loss of trypsin-positive acinar cells, which was also confirmed by western blotting. The serum of AIP patients contained high titers of autoantibodies against the trypsinogens PRSS1 and PRSS2 but not against PRSS3. In addition, there were autoantibodies against the trypsin inhibitor PSTI (the product of the SPINK1 gene). In the pancreas of AIP animals, it was found similar protein patterns and a reduction in trypsinogen. These data indicate that the immune-mediated process characterizing AIP involves pancreatic acinar cells and their secretory enzymes such as trypsin isoforms [331].

Association with myelodysplastic syndrome

A 65-year-old man with myelodysplastic syndrome (MDS) was admitted for progressive jaundice. Diffuse pancreatic swelling and stricture of the main pancreatic duct were observed with elevated serum levels of direct bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, gammaGTP and amylase, and impaired glucose tolerance. Serum IgG and IgG4 levels were highly elevated, and both the direct antiglobulin test and platelet-associated IgG were positive. He was diagnosed with autoimmune pancreatitis associated with MDS, and biliary drainage followed by immunosuppressive therapy ameliorated the jaundice and laboratory findings. In addition to diffuse pancreatic FDG accumulation, fine incorporations of FDG to the lachrymal and submandibular glands were demonstrated, suggesting the recently proposed IgG4+ multiorgan lymphoproliferative syndrome (MOLPS). The etiology of IgG4+ MOLPS is still unknown; however, autoantibodies to blood cells in this case suggested that the autoimmune mechanism, which is caused by abnormal immune functions in MDS patients, might be involved in the pathogenesis of IgG4+ MOLPS [332].

Treatment with corticosteroids

The pathogenesis of AIP remains unclear, and the natural history and long-term prognosis of AIP are little known. Oral corticosteroid therapy for AIP is recommended. The absolute indications for steroid therapy for AIP are bile duct stenosis and accompanying systemic disease such as retroperitoneal fibrosis and diabetes mellitus. The dosage for remission induction is 30 to 40 mg/d for 1 to 2 months. The remission maintenance is needed to prevent relapse, and 5 to 10 mg/d for at least 6 months is recommended in patients who do not have complete remission. When relapse occurs, the dose used at remission induction can be readministered. Herein, it was discussed remission and relapse of AIP, focusing on corticosteroid treatment to help clinicians care for patients with AIP and to help make an ideal treatment protocol of AIP through a review of published data. It was defined remission and relapse of AIP to help investigate the natural course of AIP [333].

Autoimmune pancreatitis (AIP) responds rapidly and dramatically to steroid therapy. The aim of one study was to evaluate pancreatic exocrine and endocrine function in patients suffering from AIP both before and after steroid therapy. Fecal elastase 1 and diabetes were evaluated before steroid therapy and within 1 month of its suspension in 21 patients (13 males and 8 females, mean age 43 ± 17 years) diagnosed as having AIP between 2006 and 2008. At clinical onset, fecal elastase 1 was 107 ± 126 $\mu\text{g/g}$ stool. Thirteen patients (62 %) showed severe pancreatic insufficiency (<100 $\mu\text{g/g}$ stool), 4 (19 %) had mild insufficiency (100–200 $\mu\text{g/g}$ stool), while 4 (19 %) had normal pancreatic function (>200 $\mu\text{g/g}$ stool). Before steroids, diabetes was diagnosed in 5 patients (24 %), all of whom had very low levels of fecal elastase 1 (<19 $\mu\text{g/g}$ stool). Following steroids, fecal elastase 1 increased in all patients (237 ± 193 $\mu\text{g/g}$ stool) and observed levels were significantly higher than those seen before steroids. It was concluded that patients suffering from AIP display exocrine and/or endocrine pancreatic insufficiency at clinical onset. These insufficiencies improve after steroid therapy [334].

Corticosteroids are now widely accepted as a treatment for autoimmune pancreatitis (AIP). However, the molecular mechanism by which steroid treatment improves AIP remains largely unknown. The aim of one study was to elucidate cellular mechanisms by which corticosteroids improve both pancreatic exocrine function and histopathology in AIP. Pancreatic exocrine function was evaluated by the secretin-stimulated function test and pancreatic biopsy specimens were processed for histologic analysis at the time of diagnosis and 3 months after initiation of steroid treatment. Expression and localization of proteins was assayed by immunohistochemistry. Analysis of immunoglobulin (Ig)G4-positive plasma cells was used to verify inflammation in AIP. The number of IgG4-positive plasma cells in pancreatic sections was decreased by steroid treatment, indicating reduced inflammation. Fluid, bicarbonate (HCO_3^-), and digestive enzyme secretions all were impaired in most patients with AIP. Corticosteroids improved both bicarbonate and digestive enzyme secretion. A large fraction of the cystic fibrosis transmembrane conductance regulator (CFTR), which plays a central role in pancreatic duct HCO_3^- secretion, was mislocalized to the cytoplasm of duct cells before treatment. Corticosteroids corrected the localization of CFTR to the apical membrane, accounting for the improved HCO_3^- secretion. Steroid treatment resulted in regeneration of acinar cells, accounting for restored digestive enzyme secretion. It was concluded that corticosteroids reduce inflammation and restore both digestive enzyme and bicarbonate secretion in patients with autoimmune pancreatitis by regenerating acinar cells and correcting CFTR localization in pancreatic duct cells. Mislocalization of CFTR may explain aberrant HCO_3^- secretion in other forms of pancreatitis [335].

Autoimmune pancreatitis and sclerosing cholangitis associated with autoimmune pancreatitis respond well to steroid therapy. Some criteria used for the differential diagnosis of autoimmune pancreatitis and sclerosing cholangitis with autoimmune pancreatitis include the response to a steroid trial. A 68-year-old woman was diagnosed as having type 3 sclerosing cholangitis with autoimmune pancreatitis four years after clinical onset. Seven years after clinical onset, imaging findings revealed multiple pancreatic stones in an atrophic pancreas, stenosis of the main pancreatic duct in the head of the pancreas and upstream dilatation and a longer stretch of stenosis in the hilar hepatic region. It was tried steroid therapy in an attempt to ameliorate stenosis of both the bile duct and the pancreatic duct and prevent further progression. Neither lesion responded to steroid therapy. It was concluded that advanced-stage sclerosing cholangitis with autoimmune pancreatitis may sometimes be unresponsive to steroid therapy, and this should be borne in mind when attempting a steroid trial for the diagnosis of sclerosing cholangitis with autoimmune pancreatitis. Early administration of steroid may be important for the prevention of disease progression [336].

Effects on kidneys

Autoimmune pancreatitis (AIP) has been suggested to be complicated by tubulointerstitial nephritis or glomerulonephritis, implying that the kidney is involved as a phenotype of IgG4-positive multi-organ lymphoproliferative syndrome; however, the clinical significance of this novel entity is not well-defined. It was conducted a retrospective cohort analysis of 47 (male, 39; female, 8) AIP patients. The patients (mean age, 70 ± 10 years) had a mean observation period of 4 years. Before treatment, renal dysfunction with an eGFR of 30 and 15 ml/min/1.73 m² developed only in 11 percent (5/47) and 2 percent (1/47) of the patients, respectively. Nevertheless, urinary N-acetyl-beta-D-glucosaminidase and alpha1-microglobulin levels were elevated in 79 percent (11/14) and 31 percent (4/13) of the patients, respectively. Renal involvement in contrast-enhanced CT imaging was present in 18 percent (8/44) of the patients and was significantly associated with proteinuria and a decrease in eGFR. Furthermore, a follow-up CT study (mean, 545 days) revealed improved kidney lesions in 80 percent (4/5) of the patients after oral corticosteroid administration. In contrast, first-time kidney involvements appeared newly in 4 percent (1/28) of the patients after steroid therapy for nonrenal AIP symptoms, and in 14 percent (1/7) of the patients under no specific therapy. Although severe renal failure develops rarely in AIP patients, renal abnormalities have been significantly detected by biochemical and radiological tests. Oral corticosteroid administration, even when not targeting symptomatic nephropathy, can treat and prevent kidney involvements in AIP [337].

Extrapancreatic lesions

To clarify the frequency and clinical significance of extrapancreatic lesions in autoimmune pancreatitis the frequency and clinical characteristics of extrapancreatic lesions during the clinical course of autoimmune pancreatitis it was investigated retrospectively 64 patients. Extrapancreatic lesions occurred in 95 percent (61/64) during the clinical course of pancreatitis. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, and mediastinal or hilar lymphadenopathy were 84 percent (54/64), 23 percent (15/64), 16 percent (10/64), and 77 percent (27/35), respectively. Patients with sclerosing sialadenitis or extrapancreatic bile duct sclerosing cholangitis had a significantly higher serum immunoglobulin G concentration than those without. Univariate analysis revealed that sclerosing sialadenitis, diffuse pancreatic ductal changes, and a high serum immunoglobulin G concentration at clinical onset of autoimmune pancreatitis were significant predictive factors for relapse. Multivariate analysis revealed that diffuse pancreatic ductal changes and sclerosing sialadenitis were significant independent predictive factors for relapse of autoimmune pancreatitis [338].

Accompanied with Mikulicz's disease

Patients with autoimmune pancreatitis sometimes present with Mikulicz disease. Twenty-eight patients with autoimmune pancreatitis were divided into two groups, one with Mikulicz disease and one without it. The following factors having a possible association with the presence or absence of Mikulicz disease were investigated: sex; serum IgG and IgG4 levels; the presence or absence of antinuclear autoantibodies, jaundice, diabetes mellitus, swollen duodenal papilla, diffuse pancreatic swelling, spontaneous remission, and relapse. The Mikulicz disease and non- Mikulicz disease groups consisted of 5 and 23 patients, respectively. The results of univariate analysis revealed that patients with autoimmune pancreatitis presenting with Mikulicz disease were significantly associated with a younger onset, female predominance, high serum IgG4 titer, and diffuse pancreatic swelling. In four of the Mikulicz disease patients, onset preceded pancreatitis. It was concluded that autoimmune

pancreatitis patients presenting with Mikulicz disease tended to have different clinical features from the non- Mikulicz disease autoimmune pancreatitis patients, such as having an earlier onset, female tendency, and diffuse pancreatic swelling with a high titer of serum IgG4. Autoimmune pancreatitis with Mikulicz disease tended to precede gastroenterological events [339].

A 73-year-old woman was referred to our hospital complaining of swelling of both eyelids and submandibular glands, nausea, and weight loss. She was given a diagnosis of autoimmune pancreatitis because of a marked elevation of serum IgG and IgG4 levels and diffuse swelling of the pancreas with stenosis of the main pancreatic duct. Biopsy obtained from the lachrymal gland revealed aggregated IgG4-positive plasma cells, leading to the diagnosis of Mikulicz's disease. PET-CT revealed an accumulation of FDG in the pancreas, lachrymal glands and submandibular glands, and lymph nodes in the mediastinum, hepatic hilum, bile duct and retroperitoneum. Three months after the initiation of steroid therapy, the serum levels of IgG and IgG4 decreased and FDG accumulations of the systemic lesions were no longer visible on PET [340].

Chronic sclerosing sialadenitis (Küttner tumor)

Chronic sclerosing sialadenitis is a fibroinflammatory disease of the salivary glands, characteristically of the submandibular gland. One prior Asian study proposed that chronic sclerosing sialadenitis is a part of the spectrum of IgG4-associated disease. This association has not been confirmed in Western populations. It was therefore investigated the relationship between IgG4 and chronic sclerosing sialadenitis, and compared the histomorphologic features of this condition with those of chronic sialadenitis-not otherwise specified, Sjögren syndrome, and lymphoepithelial sialadenitis. It was evaluated 13 cases of chronic sclerosing sialadenitis and compared them with 15 cases of chronic sialadenitis-not otherwise specified, 8 lip biopsies from individuals with Sjögren syndrome, and 4 cases of lymphoepithelial sialadenitis. Immunohistochemistry for IgG, and IgG4 was carried out. IgG4-positive plasma cells were quantified and the IgG4/IgG ratio was calculated. Seven patients with chronic sclerosing sialadenitis were female and 6 were male. Their mean age was 61 years (range: 27 to 80). Twelve chronic sclerosing sialadenitis cases involved the submandibular gland (bilaterally in 3) and in one there was a parotid lesion. Three of these 12 cases had manifestations of IgG4-associated systemic disease. Morphologically these specimens had preservation of lobular architecture, hypercellular interlobular fibrosis, florid lymphoid hyperplasia, and numerous plasma cells. Obliterative phlebitis was observed in 6 cases. The histologic features of chronic sclerosing sialadenitis were reminiscent of autoimmune pancreatitis, and were either not observed or were present only focally in cases of chronic sialadenitis, Sjögren syndrome, and lymphoepithelial sialadenitis. Eleven of 12 evaluable cases showed an increased number of IgG4 plasma cells with a mean of 229/high-power field (HPF) (range 75 to 608) and an overall IgG4/IgG ratio of 0.86 (range 0.5 to 1). The only patient whose biopsy lacked IgG4-positive plasma cells had pathologic evidence of cytomegalovirus infection. Chronic sclerosing sialadenitis cases, in comparison with the other 3 groups studied, showed a significantly higher number of IgG4 positive plasma cells. Patients with chronic sialadenitis-not otherwise specified had a median number of only 16 IgG4-positive plasma cells/HPF (range 2 to 44), with an IgG4/IgG ratio of 0.14 (range 0.02 to 0.28). The Sjögren syndrome patients had a median of 1 IgG4-positive plasma cell/HPF (range 0 to 3), with an IgG4/IgG ratio of 0.02 (range 0 to 0.07). Patients with lymphoepithelial sialadenitis had a median of 0 IgG4-positive plasma cells per HPF. Chronic sclerosing sialadenitis has a characteristic morphologic appearance. This morphologic appearance, in conjunction with the elevated IgG4 expression, distinguishes chronic sclerosing sialadenitis from other inflammatory diseases of the salivary glands. Chronic sclerosing sialadenitis belongs to the spectrum of IgG4-related diseases [341].

Mimicking pancreatic cancer

It was described the clinical and radiographic features of 23 patients with AIP whose presentations mimicked pancreatic cancer. A review of clinic, radiology, and endoscopy records from a 6-year period identified patients with AIP initially suspected of having pancreatic cancer. Abdominal computed tomography (CT) with intravenous contrast, endoscopic ultrasonography (EUS), and/or ERCP was performed in each patient. The diagnosis of AIP was made histologically and/or cytologically for each patient. Nineteen of 23 patients (83 %) presented with new-onset weight loss, jaundice, or both. Nineteen (83 %) patients had CT findings worrisome for pancreatic cancer including: (1) pancreatic enlargement or focal mass, (2) regional lymphadenopathy, and/or (3) vascular invasion. Eighteen patients (78 %) had common bile duct strictures on ERCP. EUS-guided fine-needle aspiration biopsies excluded pancreatic cancer in all 22 patients who had EUS (96 %). Seven patients had surgery for continued suspicion of pancreatic cancer. Although AIP commonly presents with features suggestive of pancreatic cancer, clinical recognition of AIP with appropriate diagnostic testing including EUS with fine-needle aspiration, ERCP, IgG4 levels, and pancreatic protocol CT expedites diagnosis and can spare patients unnecessary surgery [342].

Concomittant malignancy

It was presented a case of a 67-year-old woman who developed a metastatic adenocarcinoma of the pancreatobiliary system shortly after the histologically confirmed diagnosis of autoimmune pancreatitis (AIP). This case highlights the need for increased alertness not only in differentiating AIP from pancreatic cancer at the time of diagnosis, but also to exclude concomitant malignancies of the pancreatobiliary system in the management of histologically confirmed AIP [343].

In pancreas divisum

It was reported an extremely rare case of IgG4-related sclerosing cholangitis with pancreas divisum. A 62-year-old man presented to hospital with obstructive jaundice and hilar bile duct stenosis. An inflammatory tumor was suspected due to elevated of blood IgG4 levels. Endoscopic retrograde cholangiopancreatography revealed hilar bile duct stenosis and pancreas divisum. The biopsy specimens obtained by endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) revealed inflammatory findings. Steroid hormone therapy at an initial dose of 30 mg/day resulted in dramatic improvement of the bile duct stenosis and blood chemistry data [344].

With renal involvement

Autoimmune pancreatitis (AIP) is a chronic inflammatory condition characterized by IgG4-positive plasma cells. Recent evidence suggests that it is a systemic disease affecting various organs. Tubulointerstitial nephritis has been reported in association with AIP. To investigate the incidence and types of renal involvement in patients with AIP 18 patients with no history of renal disease and a diagnosis of AIP (on the basis of histopathologic findings or a combination of characteristic imaging features, increased serum IgG4 levels, and response to steroid treatment) were included. All patients underwent computed tomography (CT) imaging and follow-up ranged from 6 months to 2 years. CT images were reviewed for the presence of renal lesions. Seven patients had renal involvement (39 %). None of the lesions was visible on non-contrast-enhanced CT scan. Parenchymal lesions appeared as multiple

nodules showing decreased enhancement (four cases). Pyelonephritis, lymphoma, and metastases were considered in the differential diagnosis. An ill-defined low-attenuation mass-like lesion was found in one patient, while diffuse thickening of the renal pelvis wall was evident in the last two cases. Renal lesions regressed in all patients after steroid treatment, the larger one leaving a fibrous cortical scar. In summary, different types of renal lesions in patients with AIP are relatively common, appearing as multiple nodules with decreased enhancement. These findings support the proposed concept of an IgG4-related systemic disease. Autoimmune disease should be suspected in cases of renal involvement in association with pancreatic focal or diffuse enlargement [345].

No Helicobacter pylori

Helicobacter pylori has been suggested to be involved in pancreatic diseases, namely autoimmune pancreatitis and pancreatic carcinoma. It was investigated the presence of conserved sequences of *Helicobacter* in pancreatic tissue and pancreatic juice from patients with chronic nonautoimmune and autoimmune pancreatitis as well as pancreatic ductal adenocarcinoma (PDAC). Thirty-five pancreatic juices collected during routine endoscopic retrograde cholangiopancreatography and 30 pancreatic tissues were studied. Nested PCR was used to detect *H. pylori* in the isolated DNA samples. In order to exclude a methodological bias, the samples were analyzed blindly in 2 different laboratories using either conventional or LightCycler PCR for *H. pylori* urease A and 16S ribosomal DNA. In the pancreas of 11 patients with autoimmune pancreatitis, no *H. pylori* DNA could be detected. Further, in none of the other tissue samples of chronic pancreatitis or PDAC could we detect any *Helicobacter* sequences. Out of the pancreatic juice samples, none demonstrated either of the 2 *Helicobacter* gene sequences investigated. Despite good scientific reasoning for an involvement of *Helicobacter* in pancreatic diseases, a direct infection of the microbial agent seems unlikely. Rather, the pathomechanism must involve molecular mimicry in autoimmune pancreatitis, or the transformation of nitric food constituents to nitrosamines in pancreatic cancer [346].

Children

It was presented a case of acute pancreatitis in a 14-year-old girl which fulfilled the diagnostic criteria of autoimmune pancreatitis (AIP) and responded to corticosteroid therapy. Imaging studies revealed that the main pancreatic duct was narrow in the head of the pancreas but had been dilated in the body at an earlier stage. The pancreatitis recurred twice when the prednisolone dose was reduced to 10 mg or less but responded each time to an increased dose and has been kept under control with low-dose prednisolone therapy for 3 years since onset. Repeated magnetic resonance cholangiopancreatography during steroid therapy revealed an improvement of the narrowing of the main pancreatic duct in the head and dilation of the duct in the body. AIP in younger patients has distinct clinical features, such as presentation with epigastralgia, back pain without jaundice, and elevated serum amylase levels. The serum level of IgG4 is rarely increased in young patients, indicating a different disease mechanism than for cases in elderly patients. Given the excellent response of this condition to steroid therapy, AIP should be considered even in young children and adolescents when the diagnosis of idiopathic pancreatitis is suggested [347].

FAMILIAL PANCREATIC CANCER

A family history of pancreatic cancer has consistently been associated with increased risk of pancreatic cancer. However, uncertainty remains about the strength of this association. Results from previous studies suggest a family history of select cancers (i.e. ovarian, breast and colorectal) could also be associated, although not as strongly, with increased risk of pancreatic cancer. It was examined the association between a family history of five types of cancer (pancreas, prostate, ovarian, breast and colorectal) and risk of pancreatic cancer using data from a collaborative nested case-control study conducted by the Pancreatic Cancer Cohort Consortium. Cases and controls were from cohort studies from the United States, Europe and China, and a case-control study from the Mayo Clinic. Analyses of family history of pancreatic cancer included 1,183 cases and 1,205 controls. A family history of pancreatic cancer in a parent, sibling or child was associated with increased risk of pancreatic cancer [multivariate-adjusted odds ratios 1.76, 95 percent confidence interval 1.19 to 2.61. A family history of prostate cancer was also associated with increased risk (OR 1.45, 95 % confidence interval 1.12 to 1.89). There were no statistically significant associations with a family history of ovarian cancer, breast cancer or colorectal cancer. The results confirm a moderate sized association between a family history of pancreatic cancer and risk of pancreatic cancer and also provide evidence for an association with a family history of prostate cancer worth further study [348].

Young-onset cancer is a hallmark of many familial cancer syndromes, yet the implications of young-onset disease in predicting risk of pancreatic cancer among familial pancreatic cancer (FPC) kindred members remain unclear. To understand the relationship between age at onset of pancreatic cancer and risk of pancreatic cancer in kindred members, it was compared the observed incidence of pancreatic cancer in 9040 individuals from 1718 kindreds enrolled in the National Familial Pancreas Tumor Registry with that observed in the general US population (Surveillance, Epidemiology, and End Results). Standardized incidence ratios (SIRs) were calculated for data stratified by familial versus sporadic cancer kindred membership, number of affected relatives, youngest age of onset among relatives, and smoking status. Competing risk survival analyses were performed to examine the risk of pancreatic cancer and risk of death from other causes according to youngest age of onset of pancreatic cancer in the family and the number of affected relatives. Risk of pancreatic cancer was significantly elevated in both FPC kindred members (SIR = 6.79, 95 % confidence interval 4.54 to 9.75) and sporadic pancreatic cancer (SPC) kindred members (SIR = 2.41, 95 % CI confidence interval 1.04 to 4.74) compared with the general population. The presence of a young-onset patient (<50 years) in the family did not alter the risk for SPC kindred members compared with those without a young-onset case in the kindred. However, risk was significantly higher among members of FPC kindreds with a young-onset case in the kindred (SIR = 9.31, 95 % confidence interval 3.42 to 20.28) than those without a young-onset case in the kindred (SIR = 6.34, 95 % confidence interval 4.02 to 9.51). Competing risk survival analyses indicated that the lifetime risk of pancreatic cancer in FPC kindreds increased with decreasing age of onset in the kindred (hazard ratio = 1.55, 95 % confidence interval 1.19 to 2.03 per year). However, youngest age of onset for pancreatic cancer in the kindred did not affect the risk among SPC kindred members. It was concluded that individuals with a family history of pancreatic cancer are at a statistically significantly increased risk of developing pancreatic cancer. Having a member of the family with a young-onset pancreatic cancer confers an added risk in FPC kindreds [349].

Utah

Several familial pancreatic cancer syndromes have been identified. However, the prevalence of familial pancreatic cancers in the general population has not been well defined. It was linked pancreatic cancer cases, identified through the Utah Cancer Registry, to the Utah Population Database, which contains genealogic data from Utah pioneers and their descendants. This database includes 1411 pancreatic adenocarcinoma cases with 3 or more generations of Utah pioneer genealogy. It was examined the familial clustering of pancreatic cancer by evaluating the relative risk (RR) of pancreatic cancer among relatives of cases. It was also used the genealogical index of familiarity to test the hypothesis of no excess relatedness among pancreatic cancer cases. The risk of pancreatic cancer was significantly increased in first-degree (RR 1.84; 95 % confidence interval 1.47 to 2.29) and second-degree (RR 1.59; 95 % confidence interval 1.31 to 2.91) relatives of individuals with pancreatic cancer. Analysis of case relatedness indicated significant excess relatedness for pancreatic cancer. More than 300 high-risk pedigrees were identified, with from 3-14 cases observed among descendants of pedigree founders. This population-based study provides evidence for increased risk of pancreatic cancer among relatives of cases and for a significantly higher average relatedness among cases than expected. These observations support the role of genetic factors in pancreatic cancer [350].

Germany

Previous small scale studies reported that deleterious BRCA2 and CDKN2a germline mutations contribute to a subset of families with inherited pancreatic cancer. As the prevalence of those mutations in the setting of familial pancreatic cancer is still not well defined for the German population, we evaluated the presence of BRCA2 and CDKN2a germline mutations in a large cohort of familial pancreatic cancer (FPC) families from the German National Case Collection for Familial Pancreatic Cancer (FaPaCa). Fifty-six FPC families with at least two-first-degree relatives with confirmed pancreatic cancer that did not fulfill the criteria of other tumor predisposition syndromes, were analyzed for BRCA2 and CDKN2a germline mutations by DHPLC and/or direct sequencing. No deleterious CDKN2a mutations were identified in our families suggesting that CDKN2a mutations are unlikely to predispose PC in FPC families without melanoma. No deleterious BRCA2 mutations, but 6 unclassified variants, were detected in our FPC collection. Combining the prevalence of deleterious BRCA2 germline mutations from our previous separate study with the data from this study we were able to much more accurately estimate the BRCA2 carrier frequency for FPC families in the German population. A total of two mutations and 6 unclassified variants (mutation range: 2.8-11.4 %) were thus identified in 70 German FPC families, indicating that the prevalence of BRCA2 mutations in the German FPC population is less frequent than previously reported [351].

Italy

In Italy, pancreatic cancer is the fifth leading cause of tumor related death with about 7000 new cases per year and a mortality rate of 95 percent. In a recent prospective epidemiological study on the Italian population, a family history was found in about 10 percent of patients suffering from a ductal adenocarcinoma of the pancreas (PDAC). A position paper from the Italian Registry for Familial Pancreatic Cancer was made to manage these high-risk individuals. Even though in the majority of high-risk individuals a genetic test to identify familial predisposition is not available, a screening protocol seems to be reasonable for subjects who have a >10-fold greater risk for the development of PDAC.

However this kind of screening should be included in clinical trials, performed in centers with high expertise in pancreatic disease, using the least aggressive diagnostic modalities [352].

OTHER HEREDITARY PANCREATIC DISEASES

Hereditary pancreatitis

Human trypsinogens are post-translationally sulfated on Tyr154 by the Golgi resident enzyme tyrosylprotein sulfotransferase-2 (TPST2). Tyrosine sulfation stimulates the autoactivation of human cationic trypsinogen. Because increased trypsinogen autoactivation has been implicated as a pathogenic mechanism in chronic pancreatitis, it was hypothesized that genetic variants of TPST2 might alter the risk for the disease. It was sequenced the 4 protein-coding exons and the adjacent intronic sequences of TPST2 in 151 subjects with chronic pancreatitis and in 169 healthy controls. The functional effect of TPST2 variants on trypsinogen sulfation was analyzed in transfected HEK 293T cells. It was detected 10 common polymorphic variants, including 6 synonymous variants and 4 intronic variants, with similar frequencies in patients and controls. None of the 8 common haplotypes reconstructed from the frequent variants showed an association with chronic pancreatitis. In addition, it was identified 5 rare TPST2 variants, which included 3 synonymous alterations, the c.458G>A (p.R153H) nonsynonymous variant and the c.-9C>T variant in the 5' untranslated region. The p.R153H variant was found in a family with hereditary pancreatitis; however, it did not segregate with the disease. In functional assays, both the p.R153H and c.-9C>T TPST2 variants catalyzed trypsinogen sulfation as well as wild-type TPST2. It was concluded that genetic variants of human TPST2 exert no influence on the risk of chronic pancreatitis [353].

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder associated with increased cancer risk. Surveillance and patient management are, however, hampered by a wide range in cancer risk estimates. It was therefore performed a systematic review to assess cancer risks in PJS patients and used these data to develop a surveillance recommendation. A systematic PubMed search was performed up to February 2009, and all original articles dealing with PJS patients with confirmed cancer diagnoses were included. Data involving cancer frequencies, mean ages at cancer diagnosis, relative risks (RRs), and cumulative risks were collected. Twenty-one original articles, 20 cohort studies, and one meta-analysis fulfilled the inclusion criteria. The cohort studies showed some overlap in the patient population and included a total of 1,644 patients; 349 of them developed 384 malignancies at an average age of 42 years. The most common malignancy was colorectal cancer, followed by breast, small bowel, gastric, and pancreatic cancers. The reported lifetime risk for any cancer varied between 37 and 93 percent, with RRs ranging from 9.9 to 18 in comparison with the general population. Age-related cumulative risks were given for any cancer and gastrointestinal, gynecological, colorectal, pancreatic, and lung cancers [354].

Peutz-Jeghers syndrome (PJS), which is characterized by multiple hamartomatous polyps of the gastrointestinal tract and mucocutaneous pigmentation, is a rare autosomal dominant disease. This syndrome is often represented as a surgical emergency with complications of the polyps such as intussusception, small bowel obstruction, bleeding, and volvulus. In particular, many studies have reported that patients with this syndrome have a high risk of gastrointestinal or extragastrointestinal malignancy including gastric, duodenal, jejunal, ileal, and colonic carcinoma as well as malignancies involving other organs such as the gallbladder, biliary tract, pancreas, tonsils, breast, and reproductive system. However, there are few reported cases of an association of this syndrome with extraintestinal malignancy. In addition to that, there is no reported case of this syndrome with malignant tumor or intraductal papillary mucinous tumor of pancreas in Korea. It was now experienced a case of

Peutz-Jeghers syndrome accompanying intraductal papillary mucinous carcinoma of the pancreas [355].

Renal-hepatic-pancreatic dysplasia

It was investigated a family where two siblings had a developmental disorder associated with polycystic dysplastic kidney disease that was incompatible with postnatal survival. Additional features observed were ductal plate malformation in the liver, dysplasia of the pancreas, and (in one individual) complete situs inversus and polymicrogyria of the cingulate gyri. The autopsy findings were compatible with renal-hepatic-pancreatic dysplasia, a condition with unknown genetic cause at the time of autopsy but with similarities to the Meckel-Gruber/Joubert group of recessive ciliopathies. Consanguinity between the parents made it likely that the mutated gene (with known or potential function in cilia) was located within a rather large region of homozygosity in the affected individuals (identical by descent). Using genetic markers (50K single nucleotide polymorphism microarrays), we found a single large homozygous region of 21.16 Mb containing approximately 200 genes on the long arm of chromosome 3. This region contained two known ciliopathy genes: NPHP3 (adolescent nephronophthisis) and IQCB1 (NPHP5), which is associated with Senior-Löken syndrome. In NPHP3, homozygosity for a deletion of the conserved splice acceptor dinucleotide (AG) preceding exon 20 was found. The finding confirms the recent report that NPHP3-null mutations cause renal-hepatic-pancreatic dysplasia. Also, the case illustrates that genes for rare and genetically heterogeneous recessive conditions may be identified by homozygosity mapping using single nucleotide polymorphism arrays in the routine clinical setting [356].

Pearson syndrome

Pearson syndrome is a rare mitochondrial disorder characterized by sideroblastic anemia and exocrine pancreas deficiency as a result of mitochondrial DNA deletion or deletion-duplication. A 21-year-old woman and 11-year-old brother who had been diagnosed with Pearson syndrome at the age of 18 and 8, respectively, and were admitted to hospital with the complaints of chronic diarrhea while using exogenous pancreas enzymes. Diarrhea was present in both for a long time and attributed to existing Pearson syndrome. Endoscopic and laboratory examinations revealed celiac disease (CD). After gluten-free diet, their symptoms were resolved. Detailed family investigation revealed that parents and the sister of the siblings were free of both Pearson syndrome and CD. There has been no previous report of the presence of these 2 disorders, Pearson syndrome and celiac disease, in the same patient [357].

Shwachman-Diamond syndrome

It was reported a 6-year-old female with congenital bone marrow failure, who was referred for allogeneic stem cell transplantation. An initial work-up in infancy had not revealed any consistent symptoms associated with an inherited syndrome. Computed tomography of her abdomen for gastrointestinal bleeding after transplantation incidentally revealed a fat-replaced pancreas and led to the molecular diagnosis of Shwachman-Diamond syndrome (SDS) in the absence of clinical exocrine pancreatic insufficiency. It was concluded that SDS may escape the clinical consensus criteria for the disease. Increased awareness of unusual presentations may allow confirming the suspected diagnosis by molecular analysis and ensure optimal management [358].

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is associated with an increased risk of tumors in the pediatric age. It was reported the case of a newborn with Beckwith-Wiedemann syndrome presenting the simultaneous occurrence of a cystic pancreatoblastoma and an adrenal neuroblastoma. Surgery was required to treat the pancreatoblastoma, and a "wait and see" policy was adopted for the neuroblastoma, which spontaneously regressed within a few months [359].

Oral-facial-digital syndrome type 1 (OFD I)

OFD I is an X-linked dominant male-lethal ciliopathy characterized by prominent external features including oral clefts, hamartomas or cysts of the tongue, and digital anomalies. Although these external features are easy to recognize and often lead to diagnosis in early childhood, visceral findings in OFD I, especially the fibrocystic liver and pancreas disease, are under-recognized. In addition, while the occurrence of polycystic kidney disease (PKD) in OFD I is well known, few patients are evaluated and monitored for this complication. We report on two adult females diagnosed with OFD I in infancy, but not evaluated for visceral involvement. In adulthood, they were incidentally found to have severe hypertension and chronic renal insufficiency due to undiagnosed PKD. A pancreatic cystic lesion, also discovered incidentally, was thought to be malignant and led to consideration of major surgery. We present NIH evaluations, including documentation of OFD I mutations, extreme beading of the intrahepatic bile ducts, pancreatic cysts, and tabulate features of reported OFD I cases having hepatic, pancreatic, and renal cystic disease. Liver and pancreas are not routinely evaluated in OFD I patients. Increased awareness and lifelong monitoring of visceral complications, particularly involving the liver, pancreas, and kidney, are essential for timely and accurate treatment [360].

Pancreatic agenesis

It was studied the genetic and clinical features of diabetic subjects in a 5-generation Michigan-Kentucky pedigree ascertained through a proband with pancreatic agenesis and homozygous for the IPF1 mutation Pro63fsx60. Diabetic and nondiabetic family members were genotyped and phenotyped. It was also carried out genetic studies to determine the history of the IPF1 mutation in the Michigan-Kentucky family and a Virginia family with the same mutation. It was identified 110 individuals; 34 are currently being treated for diabetes and 10 of these are Pro63fsX60 carriers (i.e. MODY4). Subjects with MODY as well as those with type 2 diabetes are characterized by obesity and hyperinsulinemia. Genetic studies suggest that the IPF1 mutation was inherited from an ancestor common to both the Michigan-Kentucky and Virginia families. MODY4 and type 2 diabetes in the Michigan-Kentucky pedigree were associated with obesity and hyperinsulinemia. Obesity and hyperinsulinemia have been observed occasionally in other subtypes of MODY, which suggests that hyperinsulinemia may be a general phenomenon when obesity occurs in MODY subjects. Hypoinsulinemia in nonobese MODY subjects seems to be caused by a functional defect in the beta cell. Genetic testing should be considered in multigenerational obese diabetic subjects, particularly when such families contain young diabetic members [361].

Caroli's disease

Caroli's disease is a rare congenital disorder first described by Caroli in 1958. This abnormality consists of non-obstructive, saccular or fusiform dilation of the intrahepatic bile ducts resulting in cystic lesions; similar abnormalities may also occur in the kidneys and pancreas. It was illustrate the role of enhanced mangafodipir trisodium magnetic resonance imaging in a patient with sporadic non-hereditary Caroli's disease associated with pancreatic involvement in which mangafodipir trisodium magnetic resonance imaging characterized part of the cystic liver lesions as saccular dilations of the intrahepatic bile ducts of the left lobe, allowing diagnosis of the disease. It was strongly recommend hepatobiliary magnetic resonance imaging with mangafodipir trisodium in such patients [362].

Annular pancreas

Annular pancreas (AP) is usually associated with duodenal obstruction in neonates. Pancreatitis with AP occurs frequently in adults but is rare in children. Six children who underwent duodenal bypass for annular pancreas subsequently developed recurrent pancreatitis. Three had trisomy 21. Duodenoduodenostomy had been performed in 5 patients and gastrojejunostomy in 1 patient for neonatal duodenal obstruction. All children subsequently complained of recurrent abdominal pain. Pancreatitis developed in 6 children, and magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) revealed associated pancreatobiliary anomalies such as pancreas divisum, pancreatobiliary malunion, choledochoceles, and intraluminal duodenal diverticulum. In 5 cases, surgery for recurrent or chronic pancreatitis was performed. The range of follow-up was 11 to 54 months, and all children who underwent surgery had excellent results. It was concluded that children with annular pancreas occasionally require reoperation for recurrent pancreatitis because of associated pancreatobiliary anomalies. Magnetic resonance cholangiopancreatography and ERCP provide excellent images of pancreatobiliary anomalies. Intraoperative cholangiopancreatography is also essential for accurate depiction of the ductal structure and selection of the appropriate surgical procedure [363].

Pancreas divisum

Pancreaticobiliary maljunction (PBM) is defined as a congenital anomaly in which the main pancreatic and common bile ducts are joined outside the duodenal wall and forms the long common channel. Although PBM and pancreas divisum are congenital anomalies causing pancreatitides, distinct data about the incidence of pancreas divisum in pediatric PBM has not been reported to date. One study was designed to reveal the incidence and clinical features of pancreas divisum in cases of PBM. The configurations of pancreatic ducts of 78 pediatric cases of PBM were assessed by endoscopic retrograde cholangiopancreatography (ERCP) and/or intraoperative cholangiopancreatography. Additional cannulation of the minor papilla was performed when the entire length of the main pancreatic duct was not detected with cannulation of the major papilla alone. Clear pancreatography was obtained in 71 cases out of 78 cases of PBM. Abnormal fusion of the pancreatic duct was detected in 1 case (1 %) with complete pancreas divisum. This case was asymptomatic preoperatively and for 10 years postoperatively. It was concluded that pancreas divisum exists in 1 percent of PBM. Although pancreas divisum is one of the pathogenesis of pancreatitis in pancreaticobiliary maljunction, is rarely associated with pancreaticobiliary maljunction and not always causes pancreatitis [364].

CYSTIC FIBROSIS

It was investigated differences in the volume of the pancreas in cystic fibrosis (CF) patients with and without diabetes using MRI to study the natural history of CF-related diabetes (CFRD). It was investigated 29 pancreas-insufficient adult CF patients, 13 with CFRD and 16 without diabetes. Patients with CFRD were receiving insulin therapy at the time of study. None of the non-diabetic CF patients had evidence of impaired glucose tolerance. Pancreas volume was estimated by MRI scans using T₁ weighted fat-suppression sequences and assessed by an examiner who was unaware of the patients' diabetes status. Pancreas volume of CF patients was measured and subsequently compared with that of non-CF age-matched Type 1 diabetes (T1DM) patients and healthy controls previously investigated. The two CF groups were matched for age and gender. There were no differences in spirometry values, body mass index or pancreatic exocrine function. The pancreas was visible by MRI in only 3 of 13 (23 %) patients with CFRD and in 5 of 16 (31 %) patients without diabetes, which was a not significant difference. In total, the pancreas was not detected by MRI as an anatomical entity in 21 of 29 (72 %) CF patients, irrespective of their diabetes status. When comparing the four study groups, the pancreas was significantly smaller in CF patients than in T1DM patients and healthy controls [365].

PANCREATIC STELLATE CELLS

The pancreatic secretagogue cholecystokinin (CCK) is widely thought to stimulate enzyme secretion by acinar cells indirectly via activation of the vagus nerve. It was postulated an alternative pathway for CCK-induced pancreatic secretion. It was hypothesized that neurally related pancreatic stellate cells (PSCs; located in close proximity to the basolateral aspect of acinar cells) play a regulatory role in pancreatic secretion by serving as an intermediate target for CCK and secreting the neurotransmitter acetylcholine (ACh), which, in turn, stimulates acinar enzyme secretion. To determine whether PSCs exhibit CCK-dependent ACh secretion and influence acinar enzyme secretion, primary cultures of human and rat PSCs were used. Immunoblotting and/or immunofluorescence was used to detect choline acetyltransferase (ACh synthesizing enzyme), vesicular ACh transporter (VAChT), synaptophysin, and CCK receptors 1 and 2. Synaptic-like vesicles in PSCs were identified by EM. ACh secretion by PSCs exposed to 20 pM CCK was measured by LC-MS/MS. Amylase secretion by acini [pretreated with and without the muscarinic receptor antagonist atropine (10 μ M) and cocultured with PSCs] was measured by colorimetry. PSCs express ACh synthesizing enzyme, VAChT, synaptophysin, and CCK receptors; exhibit CCK-dependent ACh secretion; and stimulate amylase secretion by acini, which is blocked by atropine. In conclusion, PSCs express the essential elements for ACh synthesis and secretion. CCK stimulates ACh secretion by PSCs, which, in turn, induces amylase secretion by acini. Therefore, PSCs may represent a previously unrecognized intrapancreatic pathway regulating CCK-induced pancreatic exocrine secretion [366].

Experimentally

Pancreatic ductal adenocarcinoma (PDAC) is often characterized by a prominent desmoplastic stroma that is induced partially by alpha-smooth muscle actin (SMA)-expressing activated pancreatic stellate cells (PSCs). One study aimed to investigate the significance of alpha-SMA expression in PDAC and the correlation between alpha-SMA mRNA levels and the patient prognosis. Methods: We obtained formalin-fixed, paraffin-embedded tissue samples from 109 patients with PDAC, who underwent pancreatectomy at our institution from 1992 to 2007. It was measured alpha-SMA mRNA levels by quantitative real-time reverse transcription-polymerase chain reaction and investigated the association of alpha-SMA mRNA expression with clinicopathologic parameters and survival time. It was also assessed the influence of activated PSCs on malignant behaviors of pancreatic cancer cells using in vitro experiments. Alpha-SMA immunoreactivity was detected exclusively in the stroma of PDAC. The group with high alpha-SMA expression showed a significantly shorter survival, as shown by univariate analysis and multivariate analysis. Alpha-SMA-expressing activated PSCs enhanced the invasiveness, proliferation, and colony formation of pancreatic cancer cells. It was concluded a quantitative analysis of alpha-SMA mRNA expression using formalin-fixed, paraffin-embedded tissue samples was useful to predict the prognosis of patients with PDAC. Activated PSCs may regulate the malignant behavior of pancreatic cancer cells [367].

It was previously reported the finding that pancreatic stellate cells (PSCs) have a phagocytic function. The aim of one study was to investigate whether engulfment of gram-positive bacteria by PSCs plays any role in the pathogenesis of pancreatic fibrosis. Rat PSCs were cultured with lipoteichoic acid (LTA) or bacteria and analyzed for alpha-smooth muscle actin expression and collagen secretion. Human pancreata were obtained from routine autopsies of 20 cases; a diagnosis of gram-positive sepsis was made in 10 of the cases (sepsis group), but sepsis had not been diagnosed in the other 10 cases (control group). Pancreatic tissue was stained with anti-LTA antibody, and the severity of pancreatic fibrosis was evaluated by histological scoring. Bacteria and LTA were internalized into the cytoplasm of cultured PSCs. Exposure to LTA or bacteria significantly increased alpha-smooth muscle actin expression

and collagen secretion. Blockade of toll-like receptor 2 significantly inhibited the increase in collagen secretion in response to LTA. There was no significant difference in the severity of pancreatic fibrosis between the sepsis group and the control group. It was concluded that the fibrogenic action of PSCs is more strongly associated with activation of the toll-like receptor-dependent pathway than it is with phagocytosis of bacteria by PSCs [368].

PANCREATIC CANCER, GENERAL ASPECTS

Despite advances on many fronts, surgeons play a leading role in the diagnosis and management of pancreatic cancer. Preoperative staging is best provided by "pancreas-protocol" abdominal CT, although endoscopic ultrasound and diagnostic laparoscopy can add value in selected patients. Surgical resection, which remains the only curative option, is now accomplished with uniformly low perioperative mortality in high-volume centers (< 3 %), although complications remain frequent. Unfortunately, the long-term prognosis for pancreatic cancer remains poor with 5-year survival rates only 15-23 percent with median survival of 13 to 18 months. Recent data from randomized trials have supported the role for adjuvant chemotherapy and questioned the traditional role of radiation. Early diagnosis and targeted multimodality treatments would appear essential to optimizing the results of surgical therapy [369].

A precise, lenient and multidisciplinary pre-therapeutic evaluation is mandatory in order to reach an optimal treatment decision in patients with pancreatic cancer. Endoscopic ultrasonography (EUS), computed tomography, laparoscopy and laparoscopic ultrasonography (LAP/LUS) are used in the diagnosis, TNM-staging and resectability assessment of these patients. Ductal adenocarcinoma is the most common tumour of the pancreas, and biopsies may be obtained during transabdominal ultrasound, EUS or LUS. However, preoperative confirmation of malignancy is not necessary unless chemo- or chemoradiation therapy is indicated [720].

Surgery remains the only hope for cure in pancreatic cancer. Postoperative morbidity and mortality below 30 percent and 5 percent, respectively, are the standard. The benefit of extended lymph node dissection and portal-mesenteric vein resection is dubious. Selected patients with locally advanced cancer may be down-staged with chemo-radiotherapy and eventually resected. Endoscopic stent placement is the preferred method to relieve biliary and/or gastrointestinal obstruction. The outcome is better for patients treated at high-volume centres than at smaller hospitals [371].

Guidelines

The evidence-based guidelines for the management of pancreatic cancer in Japan published in 2006 were revised in 2009. Results of a questionnaire survey on the 2006 version were presented with AGREE evaluation by five committee member reviewers. These guidelines are aimed to standardize the diagnostic and therapeutic algorithms for general practitioners and hospitals. Specialized institutions are to solve unanswered questions and problems by conducting appropriate clinical studies [372].

Adherence to guidelines

Pancreatic adenocarcinoma is a deadly disease; however, recent studies have suggested improved outcomes in patients with locoregional cancer. Progress was evaluated at a national level in resected patients, as measured by the proportion who received guideline-directed treatment and trends in survival. The linked Surveillance, Epidemiology, and End Results and Medicare databases were queried to identify resections for pancreatic adenocarcinoma performed between 1991 and 2002. Receipt and timing of chemotherapy and radiation with respect to time-trend were assessed. Using logistic regression, factors associated with adjuvant combination chemoradiotherapy were identified. Kaplan-Meier curves stratified by year and treatment were used to assess survival. Of the 1910 patients, 48 percent (n=915) received some form of adjuvant therapy within the first 6 months

postoperatively; 34 percent (n=658) received combination chemoradiotherapy (chemoRT). ChemoRT demonstrated a significant increase, from 29 to 38 percent. Neoadjuvant therapy was used in 6 percent (n=108) of patients; no trend was observed during the study. The in-hospital mortality rate was 8 percent (n=153 patients); no significant trend was noted. Kaplan-Meier survival, stratified by year group of diagnosis, did not change significantly over time even with comparisons of the first 3 years with the last 3 years of the study. It was concluded that adherence to guideline-directed care is improving in the United States; however, the pace is slow, and overall survival has yet to be impacted significantly. Both increased use of adjuvant therapy and the development of more promising systemic treatments are necessary to improve survival for patients with resectable pancreatic cancer [373].

Epidemiology

Ductal adenocarcinoma of the pancreas has an incidence of approximately 10 per 100,000 population per year. This number pertains to Europe, North America and parts of South America (Argentina). Men are more often afflicted than women (female:male ratio of about 1:1.5, though reports vary). There has been a very small but steady increase in the incidence over the last 50 years. Unfortunately, numbers for incidence and mortality are still practically identical for this cancer. The peak of incidence is between 60 and 80 years of age. In absolute numbers, there are 8,000 cases diagnosed annually in Germany, and 33,000 in the US. Pancreatic cancer at <40 years of age is extremely rare (2 cases per million per year), but among 80-year-olds, the incidence is about 200 new cases per 100,000 population per year. In men, carcinoma of the pancreas is the fourth most common cause of cancer death after lung, prostate and colorectal cancer. In women, it is the fifth most common cause of cancer death. Risk factors for pancreatic cancer include high-fat diet, smoking, chronic pancreatitis, primary sclerosing cholangitis, hereditary pancreatitis, family history of pancreatic cancer and diabetes mellitus. In chronic pancreatitis, the risk for pancreatic cancer is increased 20-fold, in hereditary pancreatitis it is 60-fold higher than in the general population. In a kindred with 2 first-degree relatives with pancreatic cancer, the risk for pancreatic cancer for other members of that kindred is 7-fold higher [374].

Inclusion of multiple cancers

In survival analyses using cancer registry data, second and subsequent primary cancers diagnosed in individuals are typically excluded. However, this approach may lead to biased comparisons of survival between cancer registries, or over time within a single registry. To examine the impact of including multiple primary cancers in the derivation of survival estimates using data from a population-based national cancer registry five-year relative survival estimates for persons aged 15-99 years at diagnosis were derived using all eligible primary cases from the Canadian Cancer Registry – a population-based registry containing information on cases diagnosed from 1992 onward—and then again using first primary cases only. Any pre-1992 cancer history of persons on the Canadian Cancer Registry was obtained by using auxiliary information. The inclusion of multiple cancers resulted in lower estimates of 5-year relative survival for virtually all cancers studied. The effect was somewhat attenuated by age-standardization (e.g. from 1.3 % to 1.0 % for all cancers combined), and was greatest for bladder cancer (-2.4 %) followed by oral cancer (-1.9 %) – cancers that had the first and third lowest proportions of first cancers, respectively. For the majority of cancers the difference was less than 1.0 percent. Cancers for which there was virtually no difference (e.g. lung, pancreatic, ovarian and liver) tended to be those with a poor prognosis. It was concluded that inclusion of second and subsequent primary cancers in the analysis tended to lower estimates of relative survival, the extent of which varied by cancer and age and depended in part on the proportion of first primary cancers [375].

Global epidemiology

Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of 1 million cases and an annual mortality of more than 500,000 cases. CRC is the second most common cause of cancer mortality. CRC comprises 9 percent of the global cancer burden and is the most frequent in North America, Australia, New Zealand and parts of Europe, being considered as a disease of the Western lifestyle. Despite a major decline in incidence and mortality, gastric cancer remains an important public health burden worldwide, especially in developing countries. Gastric cancer is still the fourth most common cancer and the second-third most common cause of cancer death. There is a 10-fold variation in incidence between populations at the highest and lowest risk. The incidence is particularly high in East Asia, Eastern Europe, and parts of Central and South America. Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer-related death. Regional incidence rates are highest in areas of Southern and Eastern Africa and China. A striking increase in the rates of esophageal adenocarcinoma, in contrast, stable or even decreased trends in squamous cell cancer have been observed. Pancreatic cancer ranks the fourth and fifth most common cancer in man and women, respectively, and has the lowest 5-year survival rate of any gastrointestinal tumors. Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer mortality [376].

Gender differences

Esophageal and gastric adenocarcinoma share a male predominance not seen for other adenocarcinomas of the gastrointestinal tract. These sex differences are not explained by known risk factors. An endogenous factor, such as premenopausal estrogen exposure, may act protectively in favour of women and might be detected by scrutinising sex ratios and incidence rates stratified by age. The Swedish Cancer Register was used to collect primary esophageal, gastric cardia, non-cardia gastric, colonic and pancreatic adenocarcinoma cases aged 25-84, during the study period of 1970-2006. Cases were divided into five-year age groups and crude incidence rates and male: female ratios were calculated. Evaluating potential time period effect, the corresponding results from 1970-1986 and 1987-2006 were also derived. The sex ratio for esophageal adenocarcinoma ranged from approximately 10:1 to 4:1, presenting a seemingly consistent decline with age. The sex ratio for non-cardia gastric adenocarcinoma, however, increased with age to reach 2:1 at a point one to two decades after menopause, where the ratio levelled off and eventually declined. There was no discernible time period effect concerning any type of adenocarcinoma. The ratios for gastric cardia, colonic and pancreatic adenocarcinoma were stable with age. The study indicates separate patterns of age-dependency of the sex difference in oesophageal and non-cardia gastric adenocarcinoma incidence. The non-cardia gastric adenocarcinoma pattern might be due to a protective effect during premenopausal years for the female population, while the seemingly steady decline in sex ratio in esophageal adenocarcinoma indicates a mechanism independent of menopause [377].

Impact of clinical trials

Over 18 years, 7 phase 2 trials in advanced pancreatic cancer (APC) were conducted at a cancer institute. It was sought factors that influenced the selection of patients for clinical trials and explored differences in overall survival (OS) of patients treated on clinical trials versus standard of care. The target population was patients with APC diagnosed between 1986, and 2003. Patients were divided into 3 mutually exclusive groups: treated on clinical trials at this institution, treated at the institution but not on a clinical trial, or treated at other institutions. Eight thousand two hundred thirty patients met study criteria. Significant differences were observed across the 3 groups with respect to age, race, stage, grade, and socioeconomic

status. Median OS was higher in institution's trials (9 months) than in those outside trials (5 months) or other institutions (3 months) and could not be accounted for by variations in baseline characteristics. Patients enrolled on clinical trials were younger, had better socioeconomic status, and were less often African American. Patients with APC treated at academic institutions may have longer OS than patients treated in the community. It was concluded that clinical trials seem to offer a survival advantage for patients with APC [378].

Genetics versus environmental factors: immigrants

Pancreatic cancer incidence rate varies around the world. African American, Italian, Estonian, Latvian, and Japanese men have the highest rates (incidence, about 10 per 100,000). The female rates, also approximately 10 per 100,000, are highest for Hawaiians, black Americans, and Italians. The lowest rates, less than 1 per 100,000, are seen in Algerian and Pakistanis men and women. Advancing age, tobacco smoking, high-fat and red meat diets, a very heavy alcohol drinking, obesity, chronic inflammatory pancreatitis, and diabetes seem to be related to an increased risk for pancreatic cancer. Use of smokeless tobacco, also common in Sweden, increases the risk of pancreatic cancer. Although only 5 to 10 percent of pancreatic cancer patients have an underlying germline disorder, somatic mutations may play a larger genetic role for this cancer. Whether immigration may cause any change on the risk of pancreatic cancer remains unknown. African Americans in the United States have rates that are about 50 to 90 percent higher than other ethnic groups. It was now defined the pancreatic cancer risk in immigrants to Sweden to answer the role of new environmental exposures on pancreatic cancer. The updated version of the nationwide Swedish Family-Cancer Database (2008, VIII), which has been supplied with longitudinal demographic and socioeconomic data from the national census, was used for the present study. The parental information was classified according to the country of birth. First-generation immigrants were defined as those born outside Sweden, without identified parents in the database. Because any changes in lung cancer rates might indirectly reflect the recent and past tobacco prevalence rate, risk of lung cancer was used as a surrogate for smoking frequency. The pooled estimate of the risk associated with smoking for lung cancer was provided as 9.87 and 7.58 among men and women, respectively. Concordantly, a risk of 1.63 and 1.73 among men and women, respectively, was estimated for pancreatic cancer. The database included 24,552 and 1663 cases of pancreatic cancer among the native Swedish population and immigrants, respectively. The risk of pancreatic cancer was significantly increased in North African (SIR, 2.20) and Baltic men (SIR, 1.36) compared with the native Swedish population. Only Greek men (SIR, 0.44), former Yugoslavian (SIR, 0.46), and other Asian women (SIR, 0.30) had a decreased risk. Among the large immigrant groups, it was found no significant risk difference. Significantly increased risks for lung cancer in men were seen among Europeans and some Asians immigrants, whereas only Iranians had a decreased risk (SIR, 0.53). European and some Asian women had a decreased risk; only Danishes (SIR, 2.20) and Norwegians (SIR, 1.50) had an increased risk. The birth region-specific SIRs for pancreatic cancer covaried with lung cancer in North African and Baltic men. The observed increased risk among North African and Baltic immigrants, may point to genetic predisposition for pancreatic cancer [379].

Smoking

Cigarette smoking is an established risk factor for pancreatic cancer. However, prospective data for most European countries are lacking, and epidemiologic studies on exposure to environmental tobacco smoke (ETS) in relation to pancreatic cancer risk are scarce. It was examined the association of cigarette smoking and exposure to ETS with pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). The analysis was based on 465,910 participants, including 524 first incident pancreatic cancer cases diagnosed after a median follow-up of 9 years. Estimates of risk were obtained

by Cox proportional hazard models and adjusted for weight, height, and history of diabetes mellitus. An increased risk of pancreatic cancer was found for current cigarette smokers compared with never smokers (HR 1.71; 95 % confidence interval 1.36 to 2.15), and risk increased with greater intensity and pack-years. Former cigarette smokers who quit for less than 5 years were at increased risk of pancreatic cancer (HR 1.78; 95 % confidence interval 1.23 to 2.56), but risk was comparable to never smokers after quitting for 5 years or more. Pancreatic cancer risk was increased among never smokers daily exposed to ETS (for many hours) during childhood (HR 2.61; 95 % confidence interval 0.96 to 7.10) and exposed to ETS at home and/or work (HR 1.54; 95 % confidence interval 1.00 to 2.39). These results suggest that both active cigarette smoking, as well as exposure to ETS, is associated with increased risk of pancreatic cancer and that risk is reduced to levels of never smokers within 5 years of quitting [380].

Cigarette smoking is causally related to several cancers, particularly lung cancer, yet for some cancers there are inconsistent associations. One study investigated the association of smoking with other cancers by correlating them with the regional incidence rates for lung cancer, which was used as a proxy for cigarette smoking. This ecologic approach relating cigarette smoking to cancer using a large database avoids the limitations and bias present in case-control and cohort studies. Based on the assumption that regions with a high rate of lung cancer also have a high rate of cigarette smoking, our original hypothesis is that these high-intensity regions will also have high rates of other cancers if they are associated with cigarette smoking. Linear regression and correlation analysis of regional incidence rates for lung cancer, obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, were plotted with incidence rates of other cancers to determine the association between lung cancer and the other cancers. Cancers that have a strong correlation with cigarette smoking in the literature also demonstrate a strong correlation with lung cancer. These cancers included urinary bladder, laryngeal, esophageal, colorectal, and kidney cancer. A number of cancers showed a weaker association with cigarette smoking, such as pancreatic and liver cancer. Other cancers showed no correlation, such as ovarian and prostate cancer. Cancers that respectively showed a strong or absent correlation with lung cancer in the SEER Program were similarly strongly or weakly correlated with cigarette smoking in the literature. Cancers with borderline correlations show ambiguous results or confounding variables in the literature [381].

Obesity

Standard approaches to estimating population-attributable risk (PAR) include modelling estimates of exposure prevalence and relative risk. Here, it was examined the associations between elevated BMI in post-menopausal breast, endometrial and ovarian cancers; (ii) current smoking attenuates the BMI associations in oesophageal squamous cell carcinoma, lung and pancreatic cancers; (iii) prostate screening attenuates BMI associations when all prostate cancers are considered together; and (iv) BMI is differentially associated with different histological subtypes within the same cancer group. Using secondary analyses of the aforementioned meta-analysis, it was shown 2-3-fold shifts in PAR estimations for breast and endometrial cancers depending on the MHT usage in European countries. It was also critically examine how to best handle exposures (in this example, BMI distributions) and relative risk estimates in PAR models, and argue in favour of a counterfactual approach based around BMI means. From these observations, it was developed a research framework in which to optimally evaluate future trends in numbers of new cancers attributable to excess BMI. Overall, this framework gives conservative estimates for PAR but nonetheless, the numbers of avoidable cancers across Europe through avoidance of excess weight are substantial [382].

Obesity has been proposed as a risk factor for pancreatic cancer. Pooled data were analyzed from the National Cancer Institute Pancreatic Cancer Cohort Consortium (PanScan) to study the association between prediagnostic anthropometric measures and risk of pancreatic cancer. PanScan applied a nested case-control study design and included 2170 cases and 2209 control subjects. Odds ratios and 95 percent confidence intervals were estimated using unconditional logistic regression for cohort-specific quartiles of body mass index (BMI), weight, height, waist circumference, and waist to hip ratio as well as conventional BMI categories (underweight, <18.5; normal weight, 18.5-24.9; overweight, 25.0-29.9; obese, 30.0-34.9; and severely obese, ≥ 35.0). Models were adjusted for potential confounders. In all of the participants, a positive association between increasing BMI and risk of pancreatic cancer was observed (adjusted OR for the highest vs lowest BMI quartile, 1.33; 95 % confidence interval 1.12 to 1.58). In men, the adjusted odds ratio for pancreatic cancer for the highest vs lowest quartile of BMI was 1.33 (95 % confidence interval 1.04 to 1.69), and in women it was 1.34 (95 % confidence interval 1.05 to 1.70). Increased waist to hip ratio was associated with increased risk of pancreatic cancer in women (adjusted OR for the highest vs lowest quartile, 1.87; 95 % confidence interval 1.31 to 2.69) but less so in men. These findings provide strong support for a positive association between BMI and pancreatic cancer risk. In addition, centralized fat distribution may increase pancreatic cancer risk, especially in women [383].

Higher body-mass index (BMI) has been implicated as a risk factor for developing pancreatic cancer, but its effect on survival has not been thoroughly investigated. The authors assessed the association of BMI with survival in a sample of pancreatic cancer patients and used epidemiologic and clinical information to understand the contribution of diabetes and hyperglycemia. A survival analysis using Cox proportional hazards by usual adult BMI was performed on 1861 unselected patients with pancreatic adenocarcinoma; analyses were adjusted for covariates that included clinical stage, age, and sex. Secondary analyses incorporated self-reported diabetes and fasting blood glucose in the survival model. BMI as a continuous variable was inversely associated with survival from pancreatic adenocarcinoma (hazard ratio, 1.019 for each increased unit of BMI, kg/m^2) after adjustment for age, stage, and sex. In analysis by National Institutes of Health BMI category, BMIs of 30 to 34.99 kg/m^2 (HR, 1.14; 95 % confidence interval 0.98 to 1.33), 35 to 39.99 kg/m^2 (HR 1.32, 95 % confidence interval 1.08-1.62), and ≥ 40 (HR 1.60, 95 % confidence interval 1.26 to 2.04) were associated with decreased survival compared with normal BMI of 18.5 to 24.99 kg/m^2 . Fasting blood glucose and diabetes did not affect the results. It was concluded that higher BMI is associated with decreased survival in pancreatic cancer. Although the mechanism of this association remains undetermined, diabetes and hyperglycemia do not appear to account for the observed association [384].

Physical activity

Physical activity is a modifiable lifestyle risk factor that has the potential to reduce the risk of most major cancer sites. It was examined the strength, consistency, dose-response and biological plausibility of an association between physical activity and risk of colon, breast, endometrium, lung, prostate, ovarian, gastric, rectal, pancreatic, bladder, testicular, kidney and haematological cancers. It was also estimated the population-attributable risk (PAR) for physical inactivity and cancer in 15 European countries. There is convincing or probable evidence for a beneficial effect of physical activity on the risk of colon, breast and endometrial cancers. The evidence is weaker for ovarian, lung and prostate cancers and generally either null or insufficient for all remaining cancers, including pancreatic cancer. Several hypothesised biological mechanisms include a likely effect of physical activity on insulin resistance, body composition, sex steroid hormones and a possible effect on vitamin D, adipokines, inflammation and immune function [385].

Numerous epidemiological studies have examined the association between physical activity and pancreatic cancer; however, findings from individual cohorts have largely not corroborated a protective effect. Among other plausible mechanisms, physical activity may reduce abdominal fat depots inducing metabolic improvements in glucose tolerance and insulin sensitivity, thereby potentially attenuating pancreatic cancer risk. It was performed a systematic review to examine associations between physical activity and pancreatic cancer. Six electronic databases were searched from their inception through July 2009, including MEDLINE and EMBASE, seeking observational studies examining any physical activity measure with pancreatic cancer incidence/mortality as an outcome. A random effects model was used to pool individual effect estimates evaluating highest vs. lowest categories of activity. Twenty-eight studies were included. Pooled estimates indicated a reduction in pancreatic cancer risk with higher levels of total (five prospective studies, RR 0.72; 95 % confidence interval 0.52 to 0.99) and occupational activity (four prospective studies, RR 0.75 95 % confidence interval 0.59 to 0.96). Nonsignificant inverse associations were seen between risks and recreational and transport physical activity. When examining exercise intensity, moderate activity appeared more protective (RR 0.79; 95 % confidence interval 0.52 to 1.20) than vigorous activity (RR 0.97; 95 % confidence interval 0.85 to 1.11), but results were not statistically significant and the former activity variable incorporated marked heterogeneity. Despite indications of an inverse relationship with higher levels of work and total activity, there was little evidence of such associations with recreational and other activity exposures [386].

Socioeconomy

Until now, studies examining the relationship between socioeconomic status and pancreatic cancer incidence have been inconclusive. To prospectively investigate to what extent pancreatic cancer incidence varies according to educational level within the European Prospective Investigation into Cancer and Nutrition (EPIC) study socioeconomic status at baseline was measured using the highest level of education attained. Hazard ratios by educational level and a summary index, the relative indices of inequality (RII), were estimated using Cox regression models stratified by age, gender, and center and adjusted for known risk factors. In addition, we conducted separate analyses by age, gender and geographical region. Within the source population of 407, 944 individuals at baseline, 490 first incident primary pancreatic adenocarcinoma cases were identified in nine European countries. The crude difference in risk of pancreatic cancer according to level of education was small and not statistically significant (RII 1.14, 95 % confidence interval 0.80 to 1.62). Adjustment for known risk factors reduced the inequality estimates to only a small extent. In addition, no statistically significant associations were observed for age groups (adjusted RII (≤ 60 years) 0.85, 95 % CI 0.44 to 1.64, adjusted RII (>60 years) 1.18, 95 % confidence interval 0.73 to 1.90), gender (adjusted RII (male) 1.20, 95 % confidence interval 0.68 to 2.10, adjusted RII (female) 0.96, 95 % CI 0.56 to 1.62) or geographical region (adjusted RII (Northern Europe) 1.14, 95 % confidence interval 0.81 to 1.61, adjusted RII (Middle Europe) 1.72, 95 % confidence interval 0.93 to 3.19, adjusted RII (Southern Europe) 0.75, 95 % confidence interval 0.32 to 1.80). It was concluded that despite large educational inequalities in many risk factors it was found no evidence for an association between educational level and the risk of developing pancreatic cancer in this European cohort [387].

Helicobacter bilis

Helicobacter bilis is considered to be a causative factor in the pathogenesis of biliary cancer. One study investigated the prevalence of *H. bilis* colonization of the biliary system of patients with pancreaticobiliary maljunction (PBM). Bile juice and biliary tissue samples were collected from 17 patients with PBM and 27 controls who had benign biliary disease without PBM. DNA extracted from each biliary sample was subjected to polymerase chain reaction (PCR) analysis for *H. bilis* and *Helicobacter pylori*. PCR assays revealed that 12 of the 17

patients with PBM were significantly positive for *H. bilis* DNA, compared with eight of 27 patients without PBM. Among patients with PBM, *H. bilis* DNA was identified in six of eight children, including a 2-month-old infant, and in six of nine adults. The high prevalence of *H. bilis* DNA in the biliary system of patients with PBM was independent of age, sex, common bile duct dilatation, configuration of the pancreatic and bile ducts, and amylase activity in bile. It was concluded that *H. bilis* colonization of the biliary system is extremely common in patients with PBM [388].

Allergies

Survival from pancreatic adenocarcinoma remains extremely poor, approximately 5% at 5 years. Risk factors include smoking, high body mass index (BMI), family history of pancreatic cancer, and long-standing diabetes; in contrast, allergies are associated with reduced risk. Little is known about associations between these factors and survival. We analyzed overall survival in relation to risk factors for 475 incident cases who took part in a hospital based case-control study. Analyses were conducted separately for those who did (160) and did not (315) undergo tumor resection. Kaplan-Meier methods were used to describe survival according to smoking, BMI, family history, diabetes, and presence of allergies. Cox proportional hazards models were used to adjust for covariates. There was no association with survival based on smoking, family history, or history of diabetes in either group. Among patients with resection, those with allergies showed nonstatistically significant longer survival, a median of 33 months versus 22 months. Among patients without resection, those with self-reported allergies survived significantly longer than those without allergies: 13 months compared to 10 months. Obesity was nonsignificantly associated with poorer survival, particularly in the resected group (HR = 1.62). The mechanisms underlying the association between history of allergies and improved survival are unknown [389].

NSAIDs

Non-steroidal anti-inflammatory drug (NSAID) use has been linked with pancreatic cancer risk; however, findings from epidemiological studies are inconsistent. A nested case-control study was conducted within the UK General Practice Research Database. Cases (n=1141) had a diagnosis of primary cancer of the exocrine pancreas between 1995 and 2006. Controls (n=7954) were matched with each case on general practice site, sex and year of birth. Conditional logistic regression analyses were used to generate odds ratios (OR) and 95 percent confidence intervals (CI) associated with NSAID use compared with non-use. Any use of NSAID in the 5 years before the index date or since entry into the database (excluding the year before diagnosis) was not associated with risk of pancreatic cancer; OR 0.96 (95 % confidence interval 0.84 to 1.10) and 1.03 (95 % confidence interval 0.89 to 1.19), respectively. Exposure to NSAIDs for > 773 days, in the 5 years pre-diagnosis, was associated with a reduced risk of pancreatic cancer OR 0.78 (95 % confidence interval 0.62 to 0.97). There was evidence of reduced pancreatic cancer risk with long-term use (5 years or more) of lower doses of NSAIDs OR 0.70 (95 % confidence interval 0.49 to 0.99). It was concluded that long-term exposure to NSAIDs may be associated with a reduction in risk of pancreatic cancer [390].

Radiation

The "Spiess study" follows the health of 899 persons who received multiple injections of the short-lived alpha-particle emitter ²²⁴Ra mainly between 1945 and 1955 for the treatment of tuberculosis, ankylosing spondylitis and some other diseases. In 2007, 124 persons were still alive. The most striking health effect, observed shortly after ²²⁴Ra injections, was a temporal wave of 57 malignant bone tumors. During the two most recent decades of observation, a significant excess of non-skeletal malignant diseases has become evident. Expected

numbers of cases were computed from the age, gender and calendar year distribution of person years at risk and incidence rates from the German Saarland Cancer Registry. Poisson statistics were applied to test for statistical significance of the standardized incidence ratios. Up to the end of December 2007, the total number of observed malignant non-skeletal diseases was 270 (248 specified cases of non-skeletal solid cancers and 22 other malignant diseases, among these 16 malignant neoplasms of lymphatic and hematopoietic tissue, six without specification of site) compared to 192 expected cases. Accounting for a 5-year minimum latent period and excluding 13 cases of non-melanoma skin cancer, 231 non-skeletal solid cancers were observed compared to 151 expected cases. Significantly increased cancer rates were observed for breast (32 compared to 9.7), soft and connective tissue (11 compared to 1.0), thyroid (7 compared to 1.0), liver (10 compared to 2.4), kidney (13 compared to 5.0), pancreas (9 compared to 4.1), bladder (16 compared to 8.0), and female genital organs (15 compared to 7.8) [391].

Ultraviolet irradiation

To determine if an inverse association exists between latitude, ultraviolet B (UVB) irradiance and incidence rates of pancreatic cancer worldwide multiple linear regression was used to investigate the relationship and between UVB irradiance incidence rates of pancreatic cancer and while controlling for cigarette, alcohol and sugar consumption, and proportion overweight. Serum 25-hydroxyvitamin D, 25(OH)D, levels were estimated, and their association with incidence rates also was analyzed. Incidence rates were higher at higher latitudes (R² for latitude for men, 0.51; R² for latitude for women, 0.32). Ultraviolet B irradiance also was independently inversely associated with incidence in men and women. Alcohol and cigarette consumption were positively associated with incidence in men. Alcohol and sugar consumption were positively associated with incidence rates in women. Incidence rates were half as high in countries with estimated serum 25(OH)D >30 ng/mL (75 nmol/L) than in those with \leq 30 ng/mL. The authors concluded that countries with lower UVB irradiance had higher incidence rates of pancreatic cancer in both hemispheres, with occasional exceptions [392].

Carbohydrates

High-carbohydrate diets have been linked to pancreatic cancer risk in case-control studies, but prospective studies have shown mostly null results. The authors investigated the associations of glycemic load, glycemic index, and carbohydrate intake with pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Dietary intake was assessed by using a self-administered questionnaire. Between 1998 and 2006 (median follow-up 6.5 years), 266 incident, confirmed pancreatic cancers were identified among 109,175 participants. Hazards ratios and 95 percent confidence intervals were adjusted for sex, smoking, body mass index, and total energy. Overall, elevated risks for pancreatic cancer were observed in the 90th versus 10th percentile of glycemic load (hazards ratio 1.45; 95 % confidence interval 1.05 to 2.00), available carbohydrate (HR 1.47, 95 % confidence interval 1.05 to 2.06), and sucrose (HR 1.37; 95 % confidence interval 0.99 to 1.89) intake. The positive association for available carbohydrate intake was observed during the first 4 years of follow-up (HR for more than 2 years 2.60; 95 % confidence interval 1.34, 5.06; HR for 2-4 years 1.94; 95 % confidence interval 1.06 to 3.55) but not subsequently (HR 0.86; 95 % confidence interval 0.52 to 1.44); the opposite pattern was observed for total fat and saturated fat intake. Rather than being causal, the short-term increase in pancreatic cancer risk associated with high available carbohydrate and low fat intake may be capturing dietary changes associated with subclinical disease [393].

Betel chewing

A cohort study was to assess the extent of cancer risks of betel quid chewing (without tobacco added) beyond oral cancer, as such information was limited from case-control studies. The cohort, selected from participants in a medical screening program since 1994, consisted of 177,271 adult men with 19 percent chewers of betel quid. As of 2006, out of 4,840 deaths, 1,901 cancer deaths were identified. Mortality hazard ratios (HR) were estimated by Cox proportional hazard model. Life expectancy was calculated by life table method. One-third of smokers chewed (33 %) but most of chewers smoked (90 %). Risk for all cancer doubled among chewers (HR 2.00). Risks of at least six cancer sites were increased among chewers: oral cavity (HR 12.52), esophagus (HR 5.64), liver (HR 2.27), pancreas (HR 2.67), larynx (HR 6.24), and lung (HR 2.43) with risks increased with increasing betel quid amount consumed. All-cancer age-adjusted mortality rates in Taiwan increased 25 percent, including 223 percent increase in oral cancer, during the last 20 years when chewing rate increased five- to tenfolds. Chewing on top of smoking increased the risks synergistically, and these two were responsible for at least half (50 %) of all cancer deaths among 2 million chewers in Taiwan. Life expectancy of chewers was shorter than non-chewers by 5.9 years at age 20 and 5.6 years at age 40 [394].

Coffee

Coffee consumption is a major and frequent dietary exposure in diverse cultures around the globe whose safety has been questioned. A substantial body of epidemiologic evidence, consisting of over 500 papers relating the consumption of coffee to cancer of various sites, has accumulated to date. Numerous individual, site-specific meta analyses have been undertaken at various times. However, there is no comprehensive, up-to-date overview of the entirety of the knowledge base. To address this need, one review summarized the findings of the meta analyses and recent papers on site-specific human cancers among coffee consumers. For hepatocellular and endometrial cancers, there appears to be a strong and consistent protective association; for colorectal cancer, the direction of association is borderline protective. There appears to be no association with breast, pancreatic, kidney, ovarian, prostate, or gastric cancer. Risk of bladder cancer appears to be associated with heavy coffee consumption in some populations and among men [395].

Citrus fruit consumption

Basic research and case-control studies have suggested that citrus consumption may protect against cancer. However, the protective effect has been observed from few prospective studies. One study investigated the association of citrus consumption with cancer incidence among 42,470 Japanese adults in the Ohsaki National Health Insurance Cohort, which covered an age range of 40-79 years, and was followed up from 1995 to 2003 for all-cancer and individual cancer incidence. Citrus consumption was assessed using a self-administered questionnaire. During the 323,204 person-years of follow-up, 3,398 cases were identified totally. Citrus consumption, especially daily consumption, was correlated with reduced all-cancer incidence, the RRs were 0.89 (95 % confidence interval 0.80 to 0.98) for total participants, 0.86 (95 % confidence interval 0.76 to 0.98) for males and 0.93 (95 % confidence interval 0.79 to 1.09) for females, as well as multiple cancers at individual sites, especially pancreatic (RR = 0.62, 95 % confidence interval 0.38 to 1.00). Joint effect analysis showed a reduced risk of overall cancer existed only for subjects who consumed ≥ 1 cup green tea/day (RR = 0.83, 95 % confidence interval 0.73 to 0.93) as well as for males (RR = 0.83, 95 % confidence interval 0.71 to 0.97) or females (RR = 0.82, 95 % confidence interval 0.68 to 0.99). These findings suggest that citrus consumption is associated with reduced all-cancer incidence, especially for subjects having simultaneously high green tea consumption [396].

Fatty acids and vitamins

It was examined the associations among intake of specific fatty acids and antioxidants and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Unconditional logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CI) as estimates of relative risk. Significantly positive associations were observed for high levels of the 8 individual saturated fatty acids, monounsaturated palmitoleic and oleic fatty acids and polyunsaturated linolenic acid. Inverse associations were observed for high levels of gadolic acid and omega-3 fatty acids. An inverse association was also observed for high total intake of vitamin C and of vitamin E. Although similar decreased risks were also observed for high supplemental intake of these 2 vitamins no association was observed for intake from food alone. These results support the hypotheses that a high intake of saturated and certain monounsaturated fatty acids may increase the risk of pancreatic cancer, whereas greater intake of omega-3 fatty acids, vitamins C and E may reduce the risk [397].

beta-Caroten

The effect of beta-carotene supplementation on cancer incidence has been investigated in several randomized controlled trials. The objective was now to review the effect of beta-carotene supplementation on cancer incidence in randomized trials by cancer site, beta-carotene supplementation characteristics and study population. Relevant trials were retrieved by searching PubMed (up to April 2009). Authors involved in selected studies were contacted for additional information. Thirteen publications reporting results from 9 randomized controlled trials were included. Overall, no effect of beta-carotene supplementation was observed on the incidence of all cancers combined (RR, 1.01; 95 % confidence intervall 0.98 to 1.04), pancreatic cancer (RR, 0.99; 95 % confidence interval 0.73 to 1.36), colorectal cancer, prostate cancer, breast cancer, melanoma, and non-melanoma skin cancer. The incidence of lung and stomach cancers were significantly increased in individuals supplemented with beta-carotene at 20-30 mg/day, and in smokers and asbestos workers compared to the placebo group. Beta-carotene supplementation has not been shown to have any beneficial effect on cancer prevention [398].

Vitamin D

The case for the influence of vitamin D on health, including cancer prevention, is increasingly compelling. While some are calling for increases in the Tolerable Upper Intake Level, fortification, and dietary supplementation, questions regarding dose and individual response variability continue to merit attention. Colorectal cancer risk reduction with adequate vitamin D status is well documented. Protection has also been observed for cancer at all sites, skin, prostate, and breast. At the same time, some individuals may be adversely affected by elevated 25(OH)D concentrations with respect to risk of cancers of the prostate, breast, pancreas, and esophagus, and in some cases a U- or J-shaped association has been suggested. Future research should seek to clarify if and for whom there may be an increased risk for cancer at particular sites with high 25(OH)D concentrations, and the concentrations at which risk increases. Fundamentally, prospective longitudinal studies of these relationships are warranted. The health status, life stage, adiposity, estrogen exposure, and nutritional status of study participants should be taken into account. Continued investigation is necessary to ensure that vitamin D recommendations are appropriately targeted to individuals who stand to benefit most, while protecting vulnerable subgroups from risk of overexposure [399].

The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) brought together 10 cohorts to conduct a prospective study of the association between vitamin D status, measured as serum concentrations of 25-hydroxyvitamin D (25(OH)D), and the development of 7 rarer cancer sites: endometrial, esophageal, gastric, kidney, non-Hodgkin lymphoma, ovarian, and pancreatic cancers. The cohorts come from 3 continents, with participants from a wide range of latitude who are racially diverse. Across each cancer site, there was no evidence of a protective association between higher concentrations of 25-hydroxyvitamin D (>75 nmol/L) and cancer outcome. An increased risk at very high levels (≥ 100 nmol/L) was noted for pancreatic cancer, confirming previous reports [400].

Low vitamin D status is common globally and is associated with multiple disease outcomes. Understanding the correlates of vitamin D status will help guide clinical practice, research, and interpretation of studies. Correlates of circulating 25-hydroxyvitamin D (25(OH)D) concentrations measured in a single laboratory were examined in 4,723 cancer-free men and women from 10 cohorts participating in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, which covers a worldwide geographic area. Demographic and lifestyle characteristics were examined in relation to 25(OH)D using stepwise linear regression and polytomous logistic regression. The prevalence of 25(OH)D concentrations less than 25 nmol/L ranged from 3 percent to 36 percent across cohorts, and the prevalence of 25(OH)D concentrations less than 50 nmol/L ranged from 29 percent to 82 percent. Seasonal differences in circulating 25(OH)D were most marked among whites from northern latitudes. Statistically significant positive correlates of 25(OH)D included male sex, summer blood draw, vigorous physical activity, vitamin D intake, fish intake, multivitamin use, and calcium supplement use. Significant inverse correlates were body mass index, winter and spring blood draw, history of diabetes, sedentary behavior, smoking, and black race/ethnicity. Correlates varied somewhat within season, race/ethnicity, and gender [401].

The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP), a consortium of 10 prospective cohort studies from the United States, Finland, and China, was formed to examine the associations between circulating 25-hydroxyvitamin D (25(OH)D) concentrations and the risk of rarer cancers. Cases (total $n=5,491$) included incident primary endometrial ($n=830$), kidney ($n=775$), ovarian ($n=516$), pancreatic ($n=952$), and upper gastrointestinal tract ($n=1,065$) cancers and non-Hodgkin lymphoma ($n=1,353$) diagnosed in the participating cohorts. At least 1 control was matched to each case on age, date of blood collection (1974-2006), gender, and race/ethnicity ($n=6,714$). Covariate data were obtained from each cohort in a standardized manner. The majority of the serum or plasma samples were assayed in a central laboratory using a direct, competitive chemiluminescence immunoassay on the DiaSorin LIAISON platform (DiaSorin, Inc., Stillwater, Minnesota). Masked quality control samples included serum standards from the US National Institute of Standards and Technology. Conditional logistic regression analyses were conducted using clinically defined cutpoints, with 50- <75 nmol/L as the reference category. Meta-analyses were also conducted using inverse-variance weights in random-effects models. This consortium approach permits estimation of the association between 25(OH)D and several rarer cancers with high accuracy and precision across a wide range of 25(OH)D concentrations [402].

Results from epidemiologic studies examining pancreatic cancer risk and vitamin D intake or 25-hydroxyvitamin D (25(OH)D) concentrations (the best indicator of vitamin D derived from diet and sun) have been inconsistent. Therefore, the authors conducted a pooled nested case-control study of participants from 8 cohorts within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) (1974-2006) to evaluate whether prediagnostic circulating 25(OH)D concentrations were associated with the development of pancreatic cancer. In total, 952 incident pancreatic adenocarcinoma cases occurred among participants (median follow-up, 6.5 years). Controls ($n=1,333$) were matched to each case by cohort, age, gender, race/ethnicity, date of blood draw, and follow-up time. Conditional logistic regression analysis was used to calculate smoking-, body mass index-, and diabetes-adjusted odds

ratios and 95 percent confidence intervals for pancreatic cancer. Clinically relevant 25(OH)D cutpoints were compared with a referent category of 50-<75 nmol/L. No significant associations were observed for participants with lower 25(OH)D status. However, a high 25(OH)D concentration (≥ 100 nmol/L) was associated with a statistically significant 2-fold increase in pancreatic cancer risk overall (odds ratio 2.12; 95 % confidence interval: 1.23 to 3.64). Given this result, recommendations to increase vitamin D concentrations in healthy persons for the prevention of cancer should be carefully considered [403].

Studies evaluating vitamin D status in relation to pancreatic cancer risk have yielded inconsistent results. It was prospectively followed 118 597 participants in the Nurses' Health Study and Health Professionals Follow-up Study from 1986 to 2006. It was calculated a 25-hydroxyvitamin D (25(OH)D) score from known predictors of vitamin D status for each individual and then examined the predicted 25(OH)D levels in relation to pancreatic cancer risk. Relative risks (RRs) and 95 percent confidence intervals were estimated using Cox proportional hazards models adjusted for age, sex, race, height, smoking, and diabetes. It was then further adjusted for body mass index (BMI) and physical activity in a sensitivity analysis. During 20 years of follow-up, it was identified 575 incident pancreatic cancer cases. Higher 25(OH)D score was associated with a significant reduction in pancreatic cancer risk; compared with the lowest quintile, participants in the highest quintile of 25(OH)D score had an adjusted RR of 0.65 (95 % confidence interval 0.50 to 0.86). Results were similar when it was further adjusted for BMI and physical activity. Higher 25(OH)D score was associated with a lower risk of pancreatic cancer in these two prospective cohort studies [404].

Islet amyloid polypeptide

To understand the role of islet amyloid polypeptide (IAPP) in type 2 diabetes and pancreatic cancer (PC), it was investigated the patterns of its expression and its ratio to insulin, glucagon, somatostatin and pancreatic polypeptide cells by morphometry in tissues from these two diseases in comparison to the normal pancreas. Pancreatic tissues from 11 donors (five without pancreatic disease and six with type 2 diabetes) and 11 surgical specimens from PC patients obtained from the cancer area (zone A) and the adjacent tumor-free area (zone B) were examined immunohistochemically. The size of islets, the number on beta-, alpha-, delta-, PP-, and IAPP-expressing cells and their ratios in the islets of these tissues were determined. In the normal pancreas, only 50 percent of the beta-cells while alpha- and delta-cells co-expressed IAPP only sporadically. In tissues from diabetics as well as in zone A, the number of the beta-cells and the IAPP-expressing cells was reduced significantly, while the number of alpha- and delta-cells was increased. In zone B, however, significantly more beta-cell and IAPP-expressing cells and a significantly lower number of alpha-cells were found compared to those in zone A. Significant differences were also found between the specimens from type 2 diabetics and pancreatic cancer relative to the ratios of IAPP/beta-cell, IAPP/alpha-cells and beta-cell/delta-cells. It was concluded that the morphometric data show a decrease rather than an increase in the number of IAPP-expressing cells in pancreatic cancer. Differences in abnormalities in type-2 diabetics and in zone B of PC tissue strongly argue against the role of type 2 diabetes in PC. Rather, the development of diabetes in subjects prone to pancreatic cancer could be a red flag for malignancy [405].

Serum IGF-I/IGFBP-3 molar ratio

Experimental evidence suggests that an overexpression of insulin-like growth factor (IGF)-I is implicated in human pancreatic tumors. Increased IGF-II and decreased IGF binding protein (IGFBP)-3 serum concentrations have been linked to a number of other cancers. It was conducted a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort of men and women 55 to 74 years of age at baseline to test whether

prediagnostic circulating IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio concentrations were associated with exocrine pancreatic cancer risk. Between 1994 and 2006, 187 incident cases of pancreatic adenocarcinoma occurred (follow-up of up to 12 years). Two controls (n=374), who were alive at the time the case was diagnosed, were selected for each case and matched by age, race, sex, and date of blood draw. The results were adjusted for smoking. IGF-I, IGF-II, and IGFBP-3 concentrations were not significantly associated with pancreatic cancer (highest compared with lowest quartile: OR, 1.58; 95 % confidence interval 0.91 and 2.76; OR, 0.86; 95 % confidence interval 0.49 to 1.50; and OR, 0.88; 95 % confidence interval 0.51 to 1.51; respectively). However, a significant positive trend was observed with high IGF-I/IGFBP-3 molar ratio levels (highest compared with lowest quartile: OR, 1.54; 95 % confidence interval 0.89 to 2.66). It was concluded that a higher IGF-I/IGFBP-3 molar ratio represents increased free IGF-I, which may be a risk factor for pancreatic cancer [406].

Parity (estrogen influence)

One study was undertaken to examine whether there is an association between parity and age at first birth and risk of pancreatic cancer. The study cohort consisted of all women with a record of a first and singleton childbirth in the Birth Registration System between 1978 and 1987. It was tracked each woman from the time of their first childbirth and linked their vital status with mortality database. Cox proportional hazard regression models were used to estimate the relative risks (RRs) of death from pancreatic cancer associated with parity and age at first birth. A trend of increasing risk of pancreatic cancer was seen with increasing age at first birth. The adjusted RR was 0.69 (95 % confidence interval 0.49 to 0.98) for women who born two children and 0.64 (95 % confidence interval 0.44 to 0.93) for women with three or more births, respectively, when compared with women who had given birth to only one child. There was a significant decreasing trend in the RR of pancreatic cancer with increasing parity. This study provides evidence that reproductive factors (parity and early age at first birth) may confer a protective effect on the risk of pancreatic cancer [407].

ABO blood groups

ABO blood type has been associated with various malignancies, including pancreatic cancer. The aim was to study this association using data from a hospital-based tumour registry. From the tumour registry, it was retrieved data from 15,359 cancer patients treated during 2000-2003 at the European Institute of Oncology (Milan, Italy), with defined ABO blood type. It was performed a case-control analysis, comparing the distribution of ABO blood types of patients with each specific form of cancer against that of patients with other forms of cancer. It was observed a significantly lower frequency of blood type O in patients with exocrine pancreatic cancer compared to patients with other forms of cancer (29 % vs 44 %; odds ratio, 0.53; 95 % confidence intervals 0.33 to 0.83). This association was confirmed by the meta-analysis of seven prior studies (summary relative risk, 0.79; 95 % confidence interval 0.70 to 0.90). No association was found for endocrine pancreatic cancer or for cancer originating in other organs. The data suggest that the association between ABO blood group and cancer is limited to exocrine pancreas malignancy [408].

Carriage of a non-O ABO blood group and colonization by *Helicobacter pylori* are thought to be risk factors for pancreatic cancer. It was examined these associations in a population-based case-control study of 373 case patients and 690 control subjects frequency matched on sex and age. Control subjects were selected by random-digit dialing. Seropositivity for *H pylori* and its virulence protein CagA was determined by enzyme-linked immunosorbent assay (ELISA). Increased risk of pancreatic cancer was significantly associated with non-O blood group (adjusted odds ratio 1.37; 95% confidence interval 1.02 to 1.83) and CagA-negative *H pylori* seropositivity (OR 1.68; 95 % confidence interval 1.07 to 2.66), but no

association was observed for CagA seropositivity (OR 0.77). An association between pancreatic cancer risk and CagA-negative H pylori seropositivity was found among individuals with non-O blood type but not among those with O blood type (OR 2.78; 95 % confidence interval 1.49 to 5.20; OR 1.28; 95 % confidence interval 0.62 to 2.64, respectively). The study demonstrates an association between pancreatic cancer and H pylori colonization, particularly for individuals with non-O blood types [409].

PCB and other organochlorine compounds

In exocrine pancreatic cancer (EPC) mechanistic relationships may exist among some organochlorine compounds (OCs) and mutations in the K-ras oncogene, as well as among the latter and dietary factors. To analyze the relationship between food intake and serum concentrations of OCs in EPC patients and the relative influence of food and OCs on the frequency of K-ras mutations in EPC incident cases of EPC were prospectively identified, and interviewed face-to-face during hospital admission 135 patients with data on OCs and diet, and 97 with additional information on K-ras status. OCs were measured by high-resolution gas chromatography with electron-capture detection. Consumption of milk and other dairy products was positively and significantly associated with concentrations of p,p'-DDT, PCB 138 and PCB 153. When adjusted by OCs, dairy products were no longer associated with K-ras. By contrast, after adjusting by consumption of dairy products, patients with the highest concentrations of p,p'-DDT and some PCBs remained more likely to have a K-ras-mutated EPC than patients with lower concentrations (odds ratio for upper tertile of PCB 138 5.5; 95 percent confidence interval 1.3 to 23.4). It was concluded that dairy products were a source of OCs. The association between dairy products and K-ras mutations was not independent of OCs. By contrast, the association between OCs and K-ras was not confounded by dairy products. Organochlorine compounds may be more likely to contribute to the occurrence of K-ras mutations than nutrients contained in dairy products [410].

Trihalomethanes

The objective of this study was to examine the relationship between total trihalomethanes (TTHM) levels in public water supplies and risk of pancreatic cancer and to determine whether calcium (Ca) and magnesium (Mg) levels in drinking water modify the effects of TTHM on risk to develop pancreatic cancer. A matched case-control study was used to investigate the relationship between the risk of death attributed to pancreatic cancer and exposure to TTHM in drinking water in 53 municipalities in Taiwan. All pancreatic cancer deaths in the 53 municipalities from 1998 through 2007 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Controls were deaths from other causes and were pair matched to the cancer cases by gender, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each cancer case. Data on TTHM levels in drinking water were collected from Taiwan Environmental Protection Administration. Information on the levels of Ca and Mg in drinking water was obtained from the Taiwan Water Supply Corporation. The municipality of residence for cancer cases and controls was presumed to be the source of the subject's TTHM, Ca, and Mg exposure via drinking water. Relative to individuals whose TTHM exposure level < 4.9 ppb, the adjusted OR (95 % confidence interval) for pancreatic cancer was 1.01 (0.85 to 1.21) for individuals who resided in municipalities served by drinking water with a TTHM exposure > 4.9 ppb. There was no evidence of an interaction of drinking water TTHM levels with low Ca intake via drinking water. However, it was found evidence of an interaction between drinking water TTHM concentrations and Mg intake via drinking water. The findings showed that the correlation between TTHM exposure and risk of pancreatic cancer is influenced by Mg in drinking water [411].

Incidence changes

Cancers of the digestive organs (including the oesophagus, stomach, small intestine, colon, rectum and anus, liver, gallbladder, and pancreas) constitute one-fifth of all cancer cases in the Nordic countries and is a group of diseases with diverse time trends and varying consequences for public health. In this study we examine trends in relative survival in relation to the corresponding incidence and mortality rates in the Nordic countries during the period 1964-2003. Data were retrieved from the NORDCAN database for the period 1964 to 2003, grouped into eight 5-year periods of diagnosis. The patients were followed up until the end of 2006. Analysis comprised trends in 5-year relative survival, excess mortality and age-specific relative survival. Survival following cancers of the colon and rectum has increased continuously over the observed period, yet Danish patients fall behind those in the other Nordic countries. The largest inter-country variation is seen for the rare cancers in the small intestine. There has been little increase in prognosis for patients diagnosed with cancers of the liver, gallbladder or pancreas; 5-year survival is generally below 15 percent. Survival also remains consistently low for patients with esophageal cancer, while minor increases in survival are seen among stomach cancer patients in all countries except Denmark. The concomitant incidence and mortality rates of stomach cancer have steadily decreased in each Nordic country at least since 1964. It was concluded that while the site-specific variations in mortality and survival largely reflect the extent of changing and improving diagnostic and clinical practices, the incidence trends highlight the importance of risk factor modification. Alongside the ongoing clinical advances, effective primary prevention measures, including the control of alcohol and tobacco consumption as well as changing dietary pattern, will reduce the incidence and mortality burden of digestive cancers in the Nordic countries [412].

Survival changes

Differences in Nordic cancer patient survival observed today originate from the 1970s, but were first identified in a mortality prediction from 1995. This paper provides timely comparisons of survival using NORDCAN, a database with comparable information from the Nordic cancer registries. Elucidation of the differences is important when monitoring cancer care generally and evaluating the impact of cancer plans. The NORDCAN database 1964-2003 with follow-up for death through 2006, was used to analyse incidence, mortality, and survival for all NORDCAN cancer sites. It was analysed 5-year relative survival and excess mortality rates in the first three months and 2-5 years after diagnosis. The time trends in survival 1989-2003 were largely similar between the Nordic countries with increases in 14 sites among men and 16 among women. In all countries the excess mortality rates were highest in the first three months after diagnosis, but decreased to similar levels across all countries 2-5 years after diagnosis. Comparing countries excess mortality was highest in Denmark irrespective of follow-up period. Lower survival was observed for Danish cancer patients in 23 of the 33 cancer sites in men and 26 of 35 sites in women. Low and similar levels of survival were observed for cancers of the oesophagus, lung, liver and pancreas, while an 8-10 percentage point difference in survival was found between countries for colorectal cancer. The notable differences in Nordic cancer patient survival can be linked to national variations in risk factors, co-morbidity, and the implementation of screening. Improved treatment and primary prevention, in particular the targeting of tobacco and alcohol use, is required to improve cancer control. The recently-initiated cancer plans in Denmark and Norway are yet to show an observable effect on the corresponding cancer survival [413].

France

Time trends in the incidence of pancreatic cancer vary considerably between countries. The aim of one study was to provide time trends in incidence during a 25-year period in a well-

defined French population. The cancer registry in Burgundy (France) was used to study time trends between 1981 and 2005 by sex, age, subsite, and histology. They were analyzed using an age-period cohort model. Age-standardized incidence rates increased from 5.7 (1981-1985) to 7.9 per 100,000 (2001-2005) in men and from 2.6 to 4.6 in women. The mean percentage of variation by the 5-year period was +9.9 percent (95 % confidence interval, 6.2 % to 13.6 %) and +13.4 percent (95 % confidence interval, 9.4 % to 17.5 %), respectively. The increase in incidence was higher for cancers of the tail and corpus than for cancers of the head of pancreas and for malignant pancreatic endocrine tumors than for adenocarcinomas. The cumulative risk of developing a pancreatic cancer rose from 0.51 percent for men born in 1900 to 1.13 percent for those born in 1950. It was 0.34 percent and 0.55 percent for women, respectively. It was concluded that the incidence of pancreatic cancer has increased sharply in France both by period and by birth cohort [414].

The Netherlands

Cancer incidence varies according to socioeconomic status (SES) and time trends. SES category may thus point to differential effects of lifestyle changes but early detection may also affect this. It was studied patients diagnosed in 1996-2008 and registered in the South Netherlands Cancer registry. Incidence rates and estimated annual percentage changes were calculated according to SES category, age group (25-44, 45-64 and ≥ 65) and gender. People with a low SES exhibited elevated incidence rates of cancer of the head and neck, upper airways (both sexes), gastro-intestinal tract, squamous cell skin cancer, breast (≥ 65) and all female genital, bladder, kidney and mature B-cells (all in females only), whereas prostate cancer, basal cell skin cancer (BCC) and melanoma (both except in older females) were most common among those with a high SES. During 1996-2008 inequalities increased unfavourably among higher SES people for prostate cancer, BCC (except in older women) and melanoma (at middle age), while decreasing favourably among low SES people for cancers of the oesophagus, stomach, pancreas and kidney (both in females only), breast, corpus uteri and ovary. Although those with a low SES exhibited the highest incidence rates of the most common cancers, higher risks were observed among those with high SES for melanoma and BCC (both except older females) and for prostate and breast (young females) cancer. Altogether this might also have contributed to the recent higher cancer awareness in Dutch society which is usually promoted more by patients of high SES and those who know or surround them [415].

Denmark

Improved one- and three-year survival was seen after the initiation of the National Cancer Control Plan in year 2000 in Denmark. Short follow-up and lack of five-year survival called for an update with more data. All Danish cancers cases from the period 1995-2006 were studied in four cohorts of three-year incident cases from 1995 to 2006 followed to death or to the end of 2008. Age-standardised one-, three- and five-year relative survival and excess mortality were computed. The improved one- and three-year survival was confirmed. The five-year survival increased from 38 percent in 1995-1997 to 48 percent in 2004-2006 for men, but a five percentage point increase is owed to the incidence increase of prostate cancer without changed mortality. In women the increase in survival was from 50 percent to 55 percent, i.e. a five percentage point increase. Improved five-year survival was seen for cancers of the oesophagus, colon and rectum, lung, and for hematological cancers; for women, also pancreas, ovary, brain and melanoma, and for men prostate cancer survival improved. No significant changes were seen regarding pancreatic cancer. The improved cancer survival was confirmed and it was also observed at the five-year follow-up. The excess mortality is largely present during the first year of follow-up and is a useful indicator of whether changes in diagnosis and care lead to the desired outcome. Overall survival should be interpreted in the context of major changes in recorded incidence due to the introduction of new diagnostic tools and biomarkers such as prostate-specific antigen, as such measures do not necessarily

change mortality. Whether cancer care in Denmark has reached the highest international standard remains to be proven by survival comparison to countries with adequate data for a comparative analysis [416].

Screening of a high risk population

Pancreatic cancer is a virtually uniformly fatal disease. It was aimed to determine if screening to identify curable neoplasms is effective when offered to patients at high risk. Patients at high risk of pancreatic cancer were prospectively enrolled into a screening program. Endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and genetic testing were offered by a multidisciplinary team according to each patient's risk. Fifty-one patients in 43 families were enrolled, with mean age of 52 years, 35 percent of whom were male. Of these patients, 31 underwent EUS and 33 MRI. EUS revealed two patients with pancreatic cancer (one resectable, one metastatic), five with intraductal papillary mucinous neoplasms (IPMN), seven with cysts, and six with parenchymal changes. Five had pancreatic surgery (one total pancreatectomy for pancreatic cancer, three distal and one central pancreatectomy for pancreatic intraepithelial neoplasia 2 and IPMN). A total of 24 (47 %) had genetic testing (19 for BRCA1/2 mutations, 4 for CDKN2A, 1 for MLH1/MSH2) and 7 were positive for BRCA1/2 mutations. Four extrapancreatic neoplasms were found: two ovarian cancers on prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy, one carcinoid, and one papillary thyroid carcinoma. Overall, 6 (12 %) of the 51 patients had neoplastic lesions in the pancreas and 9 (18 %) had neoplasms in any location. All were on the initial round of screening. All patients remain alive and without complications of screening. Pancreatic cancer screening for high-risk patients with a comprehensive strategy of imaging and genetics is effective and identifies curable neoplasms that can be resected. Ongoing study will better define who will benefit from screening and what screening strategy will be the most effective [417].

Screening in a palliative setting

Cancer screening has been integrated into routine primary care but does not benefit patients with limited life expectancy. It was now evaluated the extent to which patients with advanced cancer continue to be screened for new cancers. Utilization of cancer screening procedures (mammography, Papanicolaou test, prostate-specific antigen (PSA), and lower gastrointestinal endoscopy) was assessed in 87,736 fee-for-service Medicare enrollees aged 65 years or older diagnosed with advanced lung, colorectal, pancreatic, gastroesophageal, or breast cancer between 1998 and 2005, and reported to one of the Surveillance, Epidemiology, and End Results (SEER) tumor registries. Participants were followed up until death or December 31, 2007, whichever came first. A group of 87,307 Medicare enrollees without cancer were individually matched by age, sex, race, and SEER registry to patients with cancer and observed over the same period to evaluate screening rates in context. Demographic and clinical characteristics associated with screening were also investigated. For each cancer screening test, utilization rates were defined as the percentage of patients who were screened following the diagnosis of an incurable cancer. Among women following advanced cancer diagnosis compared with controls, at least 1 screening mammogram was received by 10 percent and Papanicolaou test screening was received by 6 percent. Among men following advanced cancer diagnosis compared with controls, PSA test was received by 15 percent. For all patients following advanced diagnosis compared with controls, lower GI endoscopy was received by 2 percent. Screening was more frequent among patients with a recent history of screening. It was concluded that a sizeable proportion of patients with advanced cancer continue to undergo cancer screening tests that do not have a meaningful likelihood of providing benefit [418].

Animal models

In the last 10 years, there has been a relative explosion of new rodent systems that recapitulate both genetic and cellular lesions that lead to the development of pancreatic cancer. These models now need to be considered when selecting an appropriate in vivo system to study disease etiology, cell signaling, and drug development. The majority of these evaluations have used transplantation of cancer cells and the use of carcinogens, which still maintain their value when investigating human cancer and epigenetic contributors. Xenograft models utilize cultured or primary pancreatic cancer cells that are placed under the skin or implanted within the pancreas of immunocompromised mice. Carcinogen-induced systems rely on administration of certain chemicals to generate cellular changes that rapidly lead to pancreatic cancer. Genetically modified mice are more advanced in their design in that relevant genetic mutations can be inserted into mouse genomic DNA in both a conditional and inducible manner. Generation of mice that develop spontaneous pancreatic cancer from a targeted genetic mutation is a valuable research tool, considering the broad spectrum of genes and cell targets that can be used, producing a variety of neoplastic lesions and cancer that can reflect many aspects of human pancreatic ductal adenocarcinoma [419].

Genetics and polymorphism

Insulin-like growth factor (IGF)-axis mediated signaling pathways play an important role in pancreatic cancer development and progression. It was examined whether IGF-axis gene variants are associated with clinical outcomes in pancreatic cancer by retrospectively genotyping 41 single-nucleotide polymorphisms from 10 IGF-axis genes in 333 patients with localized pancreatic adenocarcinoma and validated the findings in 373 patients with advanced disease. Associations between genotype and overall survival (OS) were evaluated using multivariable Cox proportional hazard regression models. IGF1 *8470T>C, IGF1R IVS2+46329T>C, IGFBP3 A32G, IRS1 G972R in patients with localized disease; IGF1R IVS20-3431A>G, IGF1R T766T, IGFBP3-202A>C, IRS1 IVS1+4315C>G, IRS1 G972R in patients with advanced disease; and IGF1R T766T, IGF2R L252V, IGFBP3 -202A>C, IRS1 IVS1+4315C>G, IRS1 G972R, IRS2 IVS1+5687T>C in all patients were significantly associated with OS. Two haplotypes containing the variant allele of either IRS1 G972R or IVS1-10949G>A, and an IRS2 haplotype predicted worse OS. A significant correlation between increased number of unfavorable genotypes and decreased OS was observed; patients with 0-1 (n=247), 2 (n=237), 3 (n=145), 4 (n=60), and 5-8 (n=17) unfavorable genotypes had median survival time of 24, 16, 14, 10, and 7 months, respectively. Several single-nucleotide polymorphisms of IGF1R, IGF2R, and IRS1 gene were significantly associated with tumor response to therapy and disease stage. These data suggest that individual genetic variations in the IGF axis pathway may predict worse survival in patients with pancreatic cancer. This information may identify population subgroups that could benefit from IGF-1 receptor-targeted agents [420].

Human cells divide and proliferate during the early stages of life to support development, and throughout adult life to support normal cellular turnover. Each dividing cell follows an orderly and tightly regulated series of events known as the cell cycle. This process ensures proper cellular division that maintains DNA and chromosomal integrity and responds appropriately to external signals which communicate the level of demand for new cells. In cancer, genetic mutations leading to the overexpression of proteins which support cell cycle progression, or the downregulation of proteins involved in cell cycle inhibition contributes to the dysregulated cellular division and proliferation of malignant cells. The resulting uninhibited cellular proliferation provides ample opportunity for additional genetic mutations that lead to tumor progression. In one review, it was provided a brief introduction to the cell cycle and a

discussion of the mechanism underlying the dysregulation of the cell cycle in human cancer [421].

Based on the assumption that genetic variation in carcinogen metabolism further modifies the risk of exposure-related cancers, it was studied the association of polymorphisms in the tobacco carcinogen-metabolizing gene CYP2A13 (Arg101Stop) and the alcohol-metabolizing genes ADH1B (Arg48His) and ADH1C (Ile350Val) with pancreatic cancer risk. Polymorphisms were studied by allelic discrimination. In a hospital-based case-control study, CYP2A13 variant alleles coding an inactive enzyme were found in 7 of 265 cancer-free controls and in none of 235 pancreatic carcinoma patients. Neither ADH1B or ADH1C polymorphisms alone nor their combinations showed a significant effect on pancreatic cancer risk. This study of the roles of CYP2A13, ADH1B, and ADH1C in pancreatic cancer etiology suggested that the controls may have a lower ability to bioactivate tobacco-derived procarcinogens than the cases [422].

Molecular biology

The purpose of one review was to highlight the molecular mechanisms leading to the development and progression of pancreatic ductal adenocarcinoma (PDAC) with particular emphasis on tumor cell proliferation, local invasion, and metastasis. Recent advances in the field of PDAC biology have shed light on the molecular events that trigger PDAC initiation and maintenance. It is now clear that apart from the genetic alterations within the tumor cells, interactions of the tumor with its environment are necessary for proliferation and invasion. Interestingly, a number of developmental signaling pathways are reactivated in PDAC. Progress has also been made in the understanding of the molecular events that govern the process of metastasis. Although our understanding of the mechanisms underlying PDAC pathobiology are more advanced than ever, little progress has been made in the clinical treatment of PDAC, and successful bench-to-bedside transfer of knowledge to boost new treatment options is still unsatisfying [423].

Antioxidant genes

To test the hypothesis that polymorphic variants of antioxidant genes modify the risk of pancreatic cancer, it was examined seven single-nucleotide polymorphisms (SNPs) of genes coding for superoxide dismutase (SOD) 2, glutathione S-transferase alpha 4 (GSTA4), catalase and glutathione peroxidase in 575 patients with pancreatic adenocarcinoma and 648 healthy controls in a case-control study. Information on risk factors was collected by personal interview and dietary information was collected by a self-administered food frequency questionnaire. Genotypes were determined using the Taqman method. Adjusted odds ratio (AOR) and 95 percent confidence interval were estimated by unconditional logistic regression. No significant main effect of genotype was observed. A borderline significant interaction between diabetes and SOD2 Ex2+24T>C CT/TT genotype was observed); the AORs were 0.98 for non-diabetics carrying the CT/TT genotype, 1.73 for diabetics carrying the CC genotype and 3.49 for diabetics carrying the CT/TT genotype compared with non-diabetics carrying the CC genotype. Moreover, the SOD2 -1221G>A AA genotype carriers had a significantly increased risk for pancreatic cancer among those with a low dietary vitamin E intake but decreased risk among those with a high vitamin E intake. There was a non-significant interaction between diabetes and GSTA4 Ex5-64G>A genotypes. No significant interaction between genotype with cigarette smoking or vitamin C intake was observed. These data suggest that genetic variations in antioxidant defenses modify the risk of pancreatic cancer in diabetics or individuals with a low dietary vitamin E intake [424].

B7-H1

Cancer cells develop mechanisms to evade immune cells and achieve progression. Aberrant B7-H1 and B7-1 expressions may help pancreatic carcinoma (PC) cells escape immune attack; these molecules can be considered as prognostic markers for patients with PC who have undergone radical resection. It was recruited 81 patients who had undergone radical surgical resection for PC between 1999 and 2007. To investigate the prognostic factors, it was evaluated the B7-H1 and B7-1 protein expressions in the tissue specimens of these 81 patients by immunohistochemistry and analyzed the clinical and pathological features of these specimens. B7-H1 was expressed mainly in pancreatic islets, and no B7-1 expression was detected in normal pancreatic tissues. B7-H1 and B7-1 expressions were significantly higher in pancreatic carcinoma tissues than in normal pancreatic tissues. B7-H1 and B7-1 significantly correlated with the pathological grade and tumor-node-metastasis (TNM) stage, respectively. Furthermore, B7-1-negative or B7-H1-positive statuses were prognostic indicators of poor disease-specific survival, but only combined B7-1/B7-H1 expression retained the prognostic potential after adjusting by Cox proportional hazards regression models. It was concluded that both B7-H1 and B7-1 are expressed in pancreatic cancer; these molecules are important markers for pancreatic cancer progression. Furthermore, combined B7-1/B7-H1 expression can serve as an independent prognostic marker for PC [425].

BLU

BLU was recently characterized as a novel tumor suppressor gene (TSG), and was epigenetically silenced in some tumor cell lines and primary tumor samples. High-resolution melting (HRM) analysis has been used as a novel tool for analysis of promoter methylation. We used HRM analysis to detect the methylation levels of BLU gene in 100 gastric, 100 colorectal, and 70 pancreatic cancers, and also in an equal number of adjacent normal tissues for all. The frequency of BLU methylation in all three types of cancer was significantly higher than that in normal tissues. And the expression levels of BLU were inversely correlated with methylation levels [426].

Caspase 9

A case-control study was performed to evaluate the association between a specific caspase-9 polymorphism as well as the genetic polymorphism -31G/C located in the cycle-dependent elements/cell cycle homology regions repressor element of the human survivin promoter and the risk of pancreatic cancer. Eighty patients with pancreatic cancer and 160 healthy controls were investigated for genotype and allelic frequencies of caspase-9 1263A/G and survivin -31G/C polymorphisms by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism. The G carrier group of patients and the G allele of caspase-9 1263A/G were overrepresented among the pancreatic cancer cases. With regard to tumor characteristics, a statistically significant association was detected between the survivin C carrier group of patients and the advanced T stage as well as the presence of lymph node metastasis. It was concluded that the caspase-9 G allele confers increased susceptibility to pancreatic cancer development, and the survivin C carriage status may be related to aggressive features of this malignancy [427].

Caveolin-1

The gelatinases B (MMP9) and A (MMP2) are two members of the matrix metalloproteinase (MMPs) family that are expressed in human cancer, and play a critical role in tumor cell invasion and metastasis. Caveolin-1 (Cav1) has recently been identified as a tumor metastasis modifier gene. However, the effect and mechanism of Cav1 in pancreatic

carcinoma cell invasion remain unknown. In one study, it was investigated the expression of Cav1, MMP2, and MMP9 in several different pancreatic carcinoma cell lines. The results indicated that Cav1 gene could inhibit pancreatic carcinoma cell invasion, at least in part, probably through Erk-MMP signal pathway, suggesting that the endogenous expression or re-expression of Cav1 might help therapeutically reduce their invasive potential in pancreatic carcinoma cells [428].

Cell signalling phosphoproteins

Intracellular phosphoprotein activation significantly regulates cancer progression. However, the significance of circulating phosphoproteins in the blood remains unknown. It was investigated the serum phosphoprotein profile involved in pancreatic cancer (PaCa) by a novel approach that comprehensively measured serum phosphoproteins levels, and clinically applied this method to the detection of PaCa. The serum phosphoproteins that comprised cancer cellular signal pathways were investigated by comparing sera from PaCa patients and benign controls including healthy volunteers (HVs) and pancreatitis patients. Hierarchical clustering analysis between PaCa patients and HVs revealed differential pathway-specific profiles. In particular, the components of the extracellular signal-regulated kinase (ERK) signalling pathway were significantly increased in the sera of PaCa patients compared with HVs. The positive rate of p-ERK1/2 (82 %) was found to be superior to that of CA19-9 (53 %) for early stage PaCa. For the combination of these serum levels, the area under the receiver-operator characteristics curves was showing significant ability to distinguish between the two populations in independent validation set, and between cancer and non-cancer populations in another validation set. The comprehensive measurement of serum cell signal phosphoproteins is therefore useful for the detection of PaCa [429].

Ceramides

Due to recent use of short-chain ceramides in preclinical studies, it was characterized C6-ceramide metabolism in cancer cell lines and assessed metabolic junctures for enhancing efficacy. MDA-MB-231 breast cancer cells decreased the amount of C6-ceramide metabolized to C6-sphingomyelin (C6-SM) and increased the amount metabolized to C6-glucosylceramide (C6-GC) in response to increasing concentrations. A similar trend was seen in DU-145 (prostate cancer), PANC-1 (pancreatic cancer), and LoVo (colorectal cancer) cells. KG-1 leukemia cells favored C6-SM synthesis at low (0.6 μ M) and high-dose (12 μ M) C6-ceramide. Partnering C6-ceramide with tamoxifen, a P-glycoprotein antagonist that impedes ceramide glycosylation, was an effective regimen for enhancing cytotoxicity in cells. Experiments to assess the mechanism of cell death using KG-1 cells showed that tamoxifen inhibited synthesis of C6-GC and C6-SM from C6-ceramide by 80% and 50%, respectively, which was accompanied by enhanced apoptosis. Radiolabeling of KG-1 cells with [³H]palmitic acid produced a 2-fold increase in ³H-long-chain ceramides when unlabeled C6-ceramide was added and a 9-fold increase when C6-ceramide and tamoxifen were added. The increase in ³H-palmitate radiolabeling of long-chain ceramides was blocked by inclusion of a ceramide synthase inhibitor; however, inhibiting synthesis of long-chain ceramide did not rescue cells. These studies show that tamoxifen enhances the apoptotic effects of C6-ceramide. The proposed mechanism involves blocking short-chain ceramide anabolism to favor hydrolysis and generation of sphingosine. It was proposed that use of tamoxifen and other P-glycoprotein antagonists can be an effective means for enhancing cytotoxic potential of short-chain ceramides in the treatment of cancer [430].

Chromosome aberrations

Pancreatic cancer is a devastating disease with an extremely poor prognosis, and thus, there is a great need for better diagnostic and therapeutic tools. The 19q13 chromosomal locus is

amplified in several cancer types, including pancreatic cancer, but the possible clinical significance of this aberration remains unclear. It was used fluorescence in situ hybridization on tissue microarrays containing 357 primary pancreatic tumors, 151 metastases, and 24 local recurrences as well as 120 cancer cell lines from various tissues to establish the frequency of the 19q13 amplification and to find potential correlations to clinical parameters including patient survival. Copy number increases were found in 12 percent of the primary pancreatic tumors and 9 percent of the cell lines, including those derived from bladder, colorectal, ovarian, and thyroid carcinomas. Copy number changes were significantly linked to high grade and stage tumors, and the average survival time of patients with 19q13 amplification was shorter than that of those without this aberration. The findings revealed recurrent 19q13 amplification in pancreatic cancer and involvement of the same locus as in bladder, colorectal, ovarian, and thyroid carcinomas. More importantly, the 19q13 amplifications were associated with poor tumor phenotype and showed a trend toward shorter survival [431].

Circulating endothelial cells

Circulating endothelial cells (CEC) and bone marrow-derived endothelial progenitors (ECP) play important roles in tumor growth and have been proposed as non-invasive markers of angiogenesis. However, CEC and ECP levels have not been investigated in pancreatic carcinoma patients. Using four-color flow cytometry procedures, we evaluated the count of resting (rCEC) and activated (aCEC) endothelial cells and ECP in the peripheral blood of pancreatic carcinoma patients before and after chemotherapy, consisting of gemcitabine (GEM) alone or in combination with oxaliplatin (OX), or with 5-fluorouracil (5-FU). We also correlated CEC and ECP levels with plasma levels of relevant angiogenic factors, such as vascular endothelial growth factor (VEGF)-A, VEGF-D, angiopoietin (Angio)-1, and chemokine C-X-C motif ligand (CXCL)12, measured by ELISA, and with clinical features of pancreatic cancer. The aCEC, rCEC, ECP, and VEGF-A plasma levels were significantly higher in locally-advanced and metastatic patients than controls. Both ECP and VEGF-A levels correlated positively with disease stage and inversely with patient's overall survival. Measurements after the treatment course showed that VEGF-A plasma concentrations and ECP counts had decreased significantly. In particular, VEGF-A and rCEC were significantly down after treatment with GEM alone or in combination with OX. No significant differences in terms of circulating angiogenic factor or endothelial cell subtype levels were found between responders (patients entering partial remission or with stable disease) and non-responders (patients with progressive disease) [432].

Claudin

A comparison was made between pancreatic ductal adenocarcinoma (PDAC), pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous carcinoma (IPMC) in order to understand the association between several markers and malignant potential. Fifteen surgically resected PDACs and four IPMCs were subjected to immunohistochemistry with primary antibodies to Ki-67, p53, MUC2, Gli-1, and claudin-18 (CLDN18). Ki-67, p53, MUC2, Gli-1 and CLDN18 were positive in 6 (50 %), 10 (67 %), 0 (0 %), 4 (27 %), and 6 (40 %) of the 15 PDACs, respectively. Low- to high-grade PanIN complexes were found in 2 out of the 15 PDACs. Gli-1 was continuously expressed in low- and high-grade PanINs. CLDN18 was specifically expressed in high-grade PanINs, whereas the corresponding invasive tubules did not express CLDN18. p53 was positively stained in one of the 4 IPMCs in which minimally invasive tubular type carcinomas were observed. Ki-67 and CLDN18 were positively stained in all 4 IPMCs. CLDN18 was specifically expressed in intestinal-type components of IPMCs. It was concluded that claudin 18 is involved in intestinal-type epithelial differentiation in the progression of IPMCs, contradicting the previous knowledge of its specificity in gastric epithelial differentiation [433].

Cyclins A and B1

The aim of one study was to compare the expression levels of the cyclins and the differentiation-related factors in pancreatic neoplasms. The expression levels of cyclins A and B1, E1A-like inhibitor of differentiation 1 (EID-1), p300, 3'-5'-cyclic sdenosine monophosphate response element binding protein (CREB), and acetylated histone H3 (AcH3) in ordinary ductal carcinoma (ODC) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas were investigated. More cells positive for cyclin A and EID-1 were present in the ODC than in the IPMNs. Cells positive for both cyclins and EID-1 were observed more frequently in invasive carcinoma derived from the IPMN than from the IP mucinous carcinoma. Multivariate regression analysis revealed that EID-1 and cyclin A overexpressions were independent factors associated with poor prognosis. Overall survival was significantly lower in ODC patients with overexpressions of cyclin A, EID-1, and AcH3 than in those without such overexpressions. There were significant differences in the survival curves between patients with ODC and invasive carcinoma derived from IPMN, regarding high frequency for cyclin A or B1. These results indicated that the expressions of cyclins A and B1, EID-1, and AcH3 may be correlated with a malignant potential in IPMNs. Invasive carcinoma derived from IPMN may be slow growing as compared with ODC [434].

EGFR

Epidermal growth factor receptor (EGFR) intron 1 has a polymorphic region of CA repeats that is believed to be associated with increased EGFR expression, tumor aggressiveness, and worse survival in cancer patients. A large population of pancreatic adenocarcinoma patients was investigated to evaluate this polymorphism as a potential prognostic marker of clinical outcome. Deoxyribonucleic acid obtained from 50 resected pancreatic adenocarcinomas and from 85 diagnostic endoscopic ultrasound-guided fine-needle aspiration procedures corresponding to patients with unresectable tumors was included. The correlation between CA repeat length and EGFR messenger ribonucleic acid levels was also examined. Analysis of the 135 patients revealed no correlation between EGFR intron 1 CA repeat length and tumor stage. There was no difference in overall patient survival when stratified by allele length. A correlation between EGFR intron 1 length and EGFR transcript and protein levels could not be established. It was concluded that the length of the EGFR intron 1 CA repeats does not correlate with levels of EGFR expression and cannot be used as marker of clinical prognosis in pancreatic cancer patients [435].

EP300

Genetic and epigenetic alterations during development of pancreatic ductal adenocarcinomas are well known. One study investigated genetic and epigenetic data together with tumor biology to find specific alterations responsible for metastasis formation. Using 16 human pancreatic cancer cell lines in a murine orthotopic model, local infiltration and metastatic spread were assessed by standardized dissemination scores. The cell lines were further classified into 3 hierarchical groups according to their metastatic potential. Their mRNA and microRNA (miRNA) expression was profiled via mRNA-microarray as well as Taqman Low Density Array, and validated by single quantitative RT-PCR and Western blotting. In the highly metastatic group, a significant induction of EP300 targeting miRNAs miR-194 (fold change: 26.9), miR-200b (fold change: 61.7), miR-200c (fold change: 19.4) and miR-429 (fold change: 21.7) was detected. Corresponding to this, decreased expression of EP300 mRNA and protein were detected in the highly metastatic pancreatic cancer cell lines with liver metastases compared to the nonmetastatic or marginally metastatic cell lines, while no correlation with local tumor growth was found. In conclusion, epigenetic alterations with upregulated EP300 targeting miRNAs miR-194, miR-200b, miR-200c and miR-429 are related to reduced EP300 mRNA and protein in ductal pancreatic cancer [436].

Epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) is a physiologic process that allows morphological and genetic changes of carcinoma cells from an epithelial to a mesenchymal phenotype, which is the basis of the high metastatic potential of pancreatic cancer cells. EMT is triggered by various tumor microenvironmental factors, including cytokines, growth factors, and chemotherapeutic agents. One review summarized the state-of-the-art knowledge on the molecular mechanisms that support pancreatic cancer EMT and the evidences that support its involvement in invasiveness/ aggressiveness, and the drug resistance of pancreatic cancer cells [437].

Ezrin

It has been suggested that ezrin activation plays a key role in the regulation of cancer metastasis. In one study, immunohistochemically investigated the expression patterns of total ezrin and its two phosphorylated forms, pEzrin(- Thr567) and pEzrin(- Tyr353), in 66 samples of invasive pancreatic carcinomas and 11 samples of normal pancreas tissues. Positive expressions of ezrin and pEzrin(- Thr567) were detected in most pancreatic ductal carcinoma tissues, significantly higher than that of pEzrin(- Tyr353). Furthermore, overexpression of pEzrin(- Tyr353) in pancreatic cancers was associated with positive lymph node metastasis, less differentiation, pAkt overexpression, and shorter survival times. pEzrin(- Tyr353) may be a potent prognosis predictor for pancreatic cancer [438].

Follicle-stimulating hormone

In adult humans, the follicle-stimulating hormone (FSH) receptor is expressed only in the granulosa cells of the ovary and the Sertoli cells of the testis. It is minimally expressed by the endothelial cells of gonadal blood vessels. It was used immunohistochemical and immunoblotting techniques involving four separate FSH-receptor-specific monoclonal antibodies that recognize different FSH receptor epitopes and in situ hybridization to detect FSH receptor in tissue samples from patients with a wide range of tumors. Immunoelectron microscopy was used to detect FSH receptor in mouse tumors. In all 1336 patients examined, FSH receptor was expressed by endothelial cells in tumors of all grades, including early T1 tumors. The tumors were located in the prostate, breast, colon, pancreas, urinary bladder, kidney, lung, liver, stomach, testis, and ovary. In specimens obtained during surgery performed to remove tumors, the FSH receptor was not expressed in the normal tissues located more than 10 mm from the tumors. The tumor lymphatic vessels did not express FSH receptor. The endothelial cells that expressed FSH receptor were located at the periphery of the tumors in a layer that was approximately 10 mm thick; this layer extended both into and outside of the tumor. Immunoelectron microscopy in mice with xenograft tumors, after perfusion with anti-FSH-receptor antibodies coupled to colloidal gold, showed that the FSH receptor is exposed on the luminal endothelial surface and can bind and internalize circulating ligands [439].

Fucosylated haptoglobin

Recent advanced techniques in glycobiology have produced a number of tumor marker candidates. As a result from the glycomic approach, it was found that fucosylated haptoglobin in sera was a possible tumor marker for pancreatic cancer (PC). Although Aleuria aurantia lectin (AAL) blotting can detect fucosylated haptoglobin, it is difficult to quantify fucosylated haptoglobin precisely. To overcome this problem, it was developed a fucosylated haptoglobin detection kit as a sandwich enzyme-linked immune sorbent assay (ELISA) using AAL and the Fab portion of anti-haptoglobin antibody. In one study, it was investigated the clinical application of this lectin-antibody ELISA kit to measure fucosylated

haptoglobin in PC. It was measured fucosylated haptoglobin in patients with PC with a lectin-antibody ELISA kit. The fucosylated haptoglobin measured with this assay was compared with lectin blotting data, and the discrepancy was analyzed by immunoprecipitation methods. The concentration of fucosylated haptoglobin was investigated with respect to the clinical stage of PC. We also measured fucosylated haptoglobin, using 397 cases of several types of cancers including PC, benign diseases, and normal controls. The sensitivity and specificity for the differential diagnosis of PC from normal controls was 50 percent and 91 percent, respectively. The results from lectin-antibody ELISA were significantly correlated with data from previous AAL blotting studies. Positive rates of fucosylated haptoglobin with this method in patients with PC were significantly higher in cases of stage IV compared with other clinical stages. Fucosylated haptoglobin was increased in several types of cancers, in which fucosylated haptoglobin was reported to increase. While certain cases showed a discrepancy in fucosylated haptoglobin concentrations between the lectin-antibody ELISA and conventional lectin blotting, this novel type of lectin-antibody ELISA might be useful for a tumor marker for pancreatic cancer [440].

GADD45

GADD45 is a family of proteins involved in DNA damage response and cell growth arrest. GADD45G was identified as an interleukin-2-induced immediate-early gene, and methylation of GADD45G was studied in various tumor cell lines and a few primary tumor samples. High-resolution melting (HRM) analysis has been used as a novel tool for analysis of promoter methylation. In the study, it was used HRM analysis to detect the methylation levels of GADD45G gene in 100 gastric cancers, 100 colorectal cancers, 70 pancreatic cancers and equal number of adjacent normal tissues. The frequency of GADD45G methylation in all three types of cancers was significantly higher than that in normal tissues. Consistent with previous reports, expression levels of GADD45G were inversely correlated with methylation levels. But it was not found significant association between GADD45G methylation status and TNM staging in all three types of cancers. In summary, application of HRM analysis to large amount of clinical samples proves to be a fast and high-throughput way to investigate the epigenetic status of GADD45G. And this is the first study to evaluate the prevalence of GADD45G methylation based on large amount of tumor samples, showing that epigenetic regulation of GADD45G was associated with carcinogenesis [441].

Hepatocyte growth factor

Previous studies suggest that serum hepatocyte growth factor (HGF) level may be a useful diagnostic and prognostic biomarker for various tumors. It was investigated the utility of plasma HGF level measurements in diagnosing periampullary cancer (PAC). Of the patients enrolled in this pilot study (n=118), 57 had PAC, 21 had benign pancreatic tumor (BPT), 20 had chronic pancreatitis (CP), and 20 were healthy controls. Plasma HGF was measured with ELISA kits. It was measured again at 10 days and 1, 2, 3, 6, and 12 months after pancreaticoduodenectomy (PD). Plasma HGF levels were significantly higher in PAC patients than in BPT patients, CP patients, or healthy controls. When a cutoff value of 1,120 pg/mL was used, 48/57 (84 %) patients with PAC were positive for elevated HGF, but only 6/20 (30 %) of patients with CP and none of the controls or patients with BPT were positive for elevated HGF. After PD, HGF levels were significantly elevated at day 10. It was concluded that plasma HGF level discriminates well between PAC and other, benign diseases. Therefore, HGF measurement could be a useful addition to the existing array of diagnostic tools for PAC pancreatic cancer. The higher postoperative value may reflect the stress of surgery [442].

K-ras

K-ras mutation in a tumour is a powerful negative predictor for treatment success. Identifying tumour K-ras mutation is complex, and could be simplified by an appropriate blood test. Clinical studies were identified in which K-ras mutation status was assessed in both blood and tumour to ascertain whether blood K-ras mutation is predictive of tumour K-ras mutation. Between 29 percent and 100 percent of patients with a tumour K-ras mutation in 11 studies presented the same mutation in peripheral blood. Only 5/272 patients presented blood K-ras mutation in the absence of the same tumour mutation, possibly due to sampling errors. K-ras mutation in blood appears to indicate K-ras mutation in tumour, while the absence of blood K-ras mutation does not prove lack of mutation in the tumour. This suggests that a blood test for the detection of tumour K-ras may be possible, and could direct cancer treatment strategies [443].

To determine the prognostic value of K-ras mutations in plasma DNA of unresectable pancreatic cancer patients' blood samples were collected from 91 patients with unresectable pancreatic cancer prior to treatment. K-ras gene was amplified from the circulating plasma DNA. Mutations were detected by direct sequencing. The relationship between the types of K-ras gene and prognosis of unresectable pancreatic cancer was evaluated. K-Ras codon 12 mutations were found in 30 of 91 (33 %) plasma DNA samples, 17 mutations were c.35G>A (p.G12D), 11 were c.35G>T (p.G12V) and only 2 were c.34G>C (p.G12R)). K-ras codon 12 mutations could significantly reflect the clinical parameters, including TNM tumor staging and liver metastasis. The median survival time of patients with K-ras mutations was significantly shorter than that of patients with wild-type K-ras gene (4 months vs 10 months). K-ras codon 12 mutation from plasma DNA was an independent negative prognostic factor for survival (hazard ratio, 7.39; 95 % confidence interval, 3.69 to 14.89). It was concluded that K-ras mutation in plasma DNA is a predictive biomarker for a poor prognosis of unresectable pancreatic cancer patients [444].

Laminin gamma-2

The distance of nerve invasion is an important prognostic factor in pancreatic cancer. The extracellular matrix (ECM) of nerve, mainly composed of laminin, collagen IV and anchoring fibrils, might affect nerve invasion. However, this relationship has not been demonstrated. One study aimed at discovering the promoting factor of nerve invasion within the tumoral ECM. An animal model was established to evaluate the distance of nerve invasion in murine sciatic nerves by intraneural injection of 6 human pancreatic cancer cell lines. mRNA expression of laminins and anchoring fibrils was compared to the distance of nerve invasion for each cancer cell line. A target molecule provided the strong association between mRNA expression and the distance of nerve invasion. To evaluate the role of a target molecule in nerve invasion, protein expression and function were examined using an animal model and surgical cases. Cancer cells with high laminin gamma2 mRNA and protein expression in their basement membranes were associated with long nerve invasion. Knockdown of laminin gamma2 in cancer cells significantly shortened nerve invasion in the animal model. In 75 patients with pancreatic cancer, a large distance of nerve invasion was associated with high expression levels of laminin gamma2 mRNA and basement membranous deposition of laminin gamma2 protein. The results indicate that laminin gamma2 plays an important role in nerve invasion. The measurement of the nerve invasion distance in the mouse nerve invasion model is useful for evaluating the molecular mechanisms of nerve invasion [445].

MicroRNA

The poor prognosis of pancreatic ductal adenocarcinoma (PDAC) is accounted for by the absence of early diagnostic markers and effective treatments. MicroRNAs inhibit the translation of their target mRNAs. The production of microRNAs is strongly altered in

cancers, but the causes of these alterations are only partially known. DNA hypermethylation is a major cause of gene inactivation in cancer. The aims were now to identify microRNAs whose gene expression is inactivated by hypermethylation in PDAC and to determine whether this hypermethylation-mediated repression is an early event during pancreatic carcinogenesis. It was also sought to investigate whether these differentially methylated regions can serve as a diagnostic marker for PDAC. MicroRNA production was measured by microarray hybridization and reverse-transcription quantitative PCR. The level of DNA methylation was measured by bisulfite mapping and semiquantitative methylation-specific PCR. It was identified 29 microRNAs encoded by genes whose expression is potentially inactivated by DNA hypermethylation. It was then focused on microRNA 148a (miR-148a) and found its production to be repressed, not only in PDAC samples but also in preneoplastic pancreatic intraepithelial neoplasia (PanIN) lesions. More importantly, it was found that hypermethylation of the DNA region encoding miR-148a is responsible for its repression, which occurs in PanIN preneoplastic lesions. Finally, it was shown that the hypermethylated DNA region encoding miR-148a can serve as an ancillary marker for the differential diagnosis of PDAC and chronic pancreatitis [446].

Aberrant DNA methylation and microRNA expression play important roles in the pathogenesis of pancreatic cancer. While interrogating differentially methylated CpG islands in pancreatic cancer, it was identified two members of miR-200 family, miR-200a and miR-200b, that were hypomethylated and overexpressed in pancreatic cancer. It was also identified prevalent hypermethylation and silencing of one of their downstream targets, SIP1 (ZFHX1B, ZEB2), whose protein product suppresses E-cadherin expression and contributes to epithelial mesenchymal transition. In a panel of 23 pancreatic cell lines, it was observed a reciprocal correlation between miR-200, SIP1, and E-cadherin expression, with pancreatic cancer-associated fibroblasts showing the opposite expression pattern to most pancreatic cancers. In Panc-1 cells, which express SIP1, have low E-cadherin expression, and do not express miR-200a or miR-200b, treatment with miR-200a and miR-200b downregulated SIP1 mRNA and increased E-cadherin expression. However, most pancreatic cancers express miR-200a and miR-200b, but this expression does not affect SIP1 expression, as the SIP1 promoter is silenced by hypermethylation and in these cancers E-cadherin is generally expressed. Both miR-200a and miR-200b were significantly elevated in the sera of pancreatic cancer and chronic pancreatitis patients compared with healthy controls, yielding receiver operating characteristic curve areas of 0.861 and 0.85, respectively. In conclusion, most pancreatic cancers display hypomethylation and overexpression of miR-200a and miR-200b, silencing of SIP1 by promoter methylation, and retention of E-cadherin expression. The elevated serum levels of miR-200a and miR-200b in most patients with pancreatic cancer could have diagnostic utility [447].

MicroRNAs (miRNAs) are a group of small non-coding RNA molecules of 17-25 nucleotides in length, predicted to control the activity of about 30 percent of all protein-coding genes in mammals. Altered expressions of miRNAs are reported in various cancers and may associate with cancer pathogenesis, apoptosis, and cell growth, thereby functioning as either tumor suppressors or oncogenes. Recent reports showed that deregulation of miRNA contribute to tumor development and progression and hence, have diagnostic and prognostic value in several human malignancies. One review discussed the current status of miRNA in pancreatic cancer development, progression, diagnosis, and therapy [448].

Micro-RNAs inhibit the translation of their target mRNAs. The production of microRNAs is strongly altered in cancers, but the causes of these alterations are only partially known. DNA hypermethylation is a major cause of gene inactivation in cancer. The aims of one study were to identify microRNAs whose gene expression is inactivated by hypermethylation in PDAC and to determine whether this hypermethylation-mediated repression is an early event during pancreatic carcinogenesis. It was also sought to investigate whether these differentially methylated regions can serve as a diagnostic marker for PDAC. MicroRNA

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MicroRNA-21 (miR-21) was reported to be overexpressed and contributes to invasion and gemcitabine resistance in pancreatic ductal adenocarcinoma (PDAC). The aim of one study was to evaluate whether miR-21 expression was associated with the overall survival (OS) of PDAC patients treated with gemcitabine and to provide mechanistic insights for new therapeutic targets. miR-21 expression was evaluated in cells (including 7 PDAC cell lines, 7 primary cultures, fibroblasts, and a normal pancreatic ductal cell line) and tissues (neoplastic specimens from 81 PDAC patients and normal ductal samples) isolated by laser microdissection. The role of miR-21 on the pharmacologic effects of gemcitabine was studied with a specific miR-21 precursor (pre-miR-21). Patients with high miR-21 expression had a significantly shorter OS both in the metastatic and in the adjuvant setting. Multivariate analysis confirmed the prognostic significance of miR-21. miR-21 expression in primary cultures correlated with expression in their respective tissues and with gemcitabine resistance. Pre-miR-21 transfection significantly decreased antiproliferative effects and apoptosis induction by gemcitabine, whereas matrix metalloproteinase (MMP)-2/MMP-9 and vascular endothelial growth factor expression were upregulated. Addition of inhibitors of phosphoinositide 3-kinase and mammalian target of rapamycin resulted in decrease of phospho-Akt and prevented pre-miR-21-induced resistance to the proapoptotic effects of gemcitabine. miR-21 expression correlated with outcome in PDAC patients treated with gemcitabine. Modulation of apoptosis, Akt phosphorylation, and expression of genes involved in invasive behavior may contribute to the role of miR-21 in gemcitabine chemoresistance and to the rational development of new targeted combinations [450].

Mutated kinases

Protein kinases are key regulators of cellular processes (such as proliferation, apoptosis and invasion) that are often deregulated in human cancers. Accordingly, kinase genes have been the first to be systematically analyzed in human tumors leading to the discovery that many oncogenes correspond to mutated kinases. In most cases the genetic alterations translate in constitutively active kinase proteins, which are amenable of therapeutic targeting. Tumours of the pancreas are aggressive neoplasms for which no effective therapeutic strategy is currently available. It was conducted a DNA-sequence analysis of a selected set of 35 kinase genes in a panel of 52 pancreatic exocrine neoplasms, including 36 pancreatic ductal adenocarcinoma, and 16 ampulla of Vater cancer. Among other changes it was found somatic mutations in ATM, EGFR, EPHA3, EPHB2, and KIT, none of which was previously described in cancers. Although the alterations identified require further experimental evaluation, the localization within defined protein domains indicates functional relevance for most of them. Some of the mutated genes, including the tyrosine kinases EPHA3 and EPHB2, are clearly amenable to pharmacological intervention and could represent novel therapeutic targets for these incurable cancers [451].

NGF

Pancreatic cancer (PCa) is characterized by neuropathic alterations which are resulting in pancreatic pain. To further characterize pancreatic neuropathy, it was aimed to analyze whether neuropathic alterations in PCa are only limited to the tumor-core or whether they are similarly encountered in neural structures in the noncancerous pancreas, to demonstrate whether PCa features neurotrophic attributes, and finally to identify responsible neurotrophic molecules. Nerve density and area were quantified in normal pancreas (NP, n=45), histologically "normal" pancreas next to pancreatic cancer (NNPCa, n=61) and PCa (n=97). Growth-associated protein-43, nerve growth factor (NGF), and Artemin expressions were assessed by Immunohistochemistry, Western-Blot, and quantitative real time polymerase chain reaction-analyses. Isolated myenteric plexus of newborn rats were exposed to NP, NNPCa, and PCa tissue extracts and supernatants of Panc1 and T3M4 cancer cells with or without Artemin and NGF depletion, followed by neurite density analysis. Dense neural networks and enlarged nerves were not only detected in PCa but were also present in NNPCa. Growth-associated protein-43, NGF, and artemin expressions were absent/weak in NP, but increased in both NNPCa and PCa and were closely associated with intrapancreatic neuropathy. PCa and NNPCa tissue extracts and Panc1/T3M4 supernatants noticeably increased neurite density in myenteric plexus-cultures, which were attenuated by depletion of NGF and Artemin. It was concluded that the neurotrophic effects of pancreatic cancer extend into the peritumoral "normal" pancreatic areas without neuro-cancer interactions. The neurotrophic characteristics of PCa can be mimicked by in vitro analyses and reveal NGF and artemin as potential key players in the generation of pancreatic neuropathy in pancreatic cancer [452].

PAM4

Pancreatic adenocarcinoma is an almost universally lethal disease, in large part, due to our inability to detect early-stage disease. Monoclonal antibody PAM4 is reactive with a unique biomarker expressed by greater than 85 percent of pancreatic adenocarcinomas. In one report, it was examined the ability of a PAM4-based immunoassay to detect early-stage disease. The PAM4-based immunoassay was used to quantitate antigen in the serum of healthy volunteers (n=19), patients with known pancreatic adenocarcinoma (n=68), and patients with a primary diagnosis of chronic pancreatitis (n=29). Sensitivity for detection of pancreatic adenocarcinoma was 82 percent, with a false-positive rate of 5 percent for healthy controls. Patients with advanced disease had significantly higher antigen levels than those with early-stage disease, with a diagnostic sensitivity of 91 percent, 86 percent, and 62 percent for stage 3/4 advanced disease, stage-2, and stage-1, respectively. It was also evaluated chronic pancreatitis sera, finding 38 percent positive for antigen; however, this was discordant with immunohistochemical findings that suggest the PAM4-antigen is not produced by inflamed pancreatic tissue. Furthermore, several of the serum-positive pancreatitis patients, for whom tissue specimens were available for pathological interpretation, had evidence of neoplastic precursor lesions. According to the authors these results suggest the use of the PAM4-serum assay to detect early-stage pancreatic adenocarcinoma, and that positive levels of PAM4-antigen are not derived from inflamed pancreatic tissues, but rather may provide evidence of subclinical pancreatic neoplasia [453].

p21 and p27

p21 (WAF1/Cip1/CDKN1A) and p27 (Kip1/CDKN1B) are members of the Cip/Kip family of cyclin-dependent kinase inhibitors, which can induce cell cycle arrest and serve as tumor suppressors. It was hypothesized that genetic variants in p21 and p27 may modify individual susceptibility to pancreatic cancer. To test this hypothesis, it was evaluated the associations of the Ser31Arg polymorphism in p21 and the Gly109Val polymorphism in p27, and their

combinations, with pancreatic cancer risk in a case-control study of 509 pathologically confirmed pancreatic adenocarcinoma patients and 462 age- and sex-matched cancer-free controls in non-Hispanic whites. It was found that the heterozygous and homozygous variant genotypes combined in a dominant model of the p21 polymorphism were associated with increased risk of pancreatic cancer compared with the homozygous wild type (adjusted odds ratio 1.70; 95 % confidence interval 1.13 to 2.55). This increased risk was more pronounced in carriers with the p27 homozygous wild type (adjusted odds ratio 2.20; 95 % confidence interval 1.32 to 3.68) and in nonsmokers (adjusted odds ratio, 2.16; 95 % confidence interval 1.14 to 4.10), although the p27 polymorphism alone was not associated with pancreatic cancer risk. These results indicate that the p21 polymorphism may contribute to susceptibility to pancreatic cancer, particularly among p27 homozygous wild-type carriers and nonsmokers [454].

PP56 (alpha-trinositol)

In one study, it was investigated whether the anti-inflammatory drug PP56 (alpha-trinositol) may improve cancer-induced metabolic disorders. It was implanted human MiaPaCa2 pancreatic cancer cells in the pancreas of 14 athymic mice for 12 weeks, using six intact littermates as normal controls. During the 12 weeks, seven tumor-cell recipients were treated with PP56 by daily injection (PPT mice). The tumor-cell recipients that were otherwise untreated were used as tumor controls (TC mice). Impaired glucose tolerance and decreased body weight gain were seen in TC but not PPT mice. When an enzyme for fatty acid beta-oxidation namely medium-chain acyl-CoA dehydrogenase (MCAD) was determined in tumor grafts; tumors from PPT mice showed more MCAD than those from TC mice. This suggests that PP56 stimulated fatty acid beta-oxidation in MiaPaCa2 cells in vivo. In keeping with this notion, PPT mice had decreased plasma free fatty acids. In vitro, it was demonstrated that MiaPaCa2 cells consumed more fatty acids in the presence of PP56. In another experiment, it was infused PP56 or vehicle in normal mice and found that PP56 decreased circulating glucose in the animals. It was also shown that PP56 increased glucose transport in L6 skeletal muscle cells in vitro. In conclusion, PP56 increases the turnover of circulating nutrients such as glucose and helps maintain energy homeostasis in mice with pancreatic cancer [455].

Smad4

Mutations of SMAD4/DPC4 are found in about 60 percent of human invasive pancreatic ductal adenocarcinomas; yet, the manner in which SMAD4 deficiency enhances tumorigenesis remains elusive. Using a Cre-LoxP approach, it was generated a mutant mouse carrying a targeted deletion of Smad4 in the pancreas. It was shown that the absence of Smad4 alone did not trigger pancreas tumor formation; however, it increased the expression of an inactivated form of Pten, suggesting a role of Pten in preventing Smad4^{-/-} cells from undergoing malignancy. To investigate this, it was disrupted both Pten and Smad4. It was shown that Pten deficiency initiated widespread premalignant lesions, and a low tumor incidence that was significantly accelerated by Smad4-deficiency. The absence of Smad4 in a Pten-mutant background enhanced cell proliferation and triggered trans-differentiation from acinar, centroacinar and islet cells, accompanied by activation of Notch1 signaling. All tumors developed in the Smad4/Pten-mutant pancreas exhibited high levels of pAKT and mTOR, and that about 50 and 83 percent of human pancreatic cancers examined showed increased pAKT and pmTOR, respectively. Besides the similarity in gene expression, the pAKT and/or pmTOR-positive human PDACs and mouse pancreatic tumors also shared some histopathological similarities. These observations indicate that Smad4/Pten-mutant mice mimic the tumor progression of human pancreatic cancers that are driven by activation of the AKT-mTOR pathway, and uncovered a synergistic action of Smad4 and Pten in repressing pancreatic tumorigenesis [456].

Syndecan-2

The aim of one study was to determine the expression and prognostic role of syndecan-2 in patients with pancreatic adenocarcinoma. Syndecan-2 expression and its relationship with established prognostic features were assessed in a series of 53 patients with pancreatic ductal adenocarcinoma. Epithelial expression was observed in 23 (43 %) and stromal in 30 (57 %) pancreatic carcinomas, respectively. In normal pancreatic tissue, the epithelial expression was moderate or strong in single or small clusters of acinar cells and negative in ductal cells. Normal pancreatic stroma did not express syndecan-2. Statistical analysis showed that stromal expression had no influence on survival but epithelial expression was positively correlated with survival time, and patients with higher epithelial syndecan-2 expression had a significantly longer survival. The results support a potential role for syndecan-2 in pancreatic carcinogenesis and cancer progression. Moreover, expression of syndecan-2 might serve as a prognostic marker [457].

Thyroid transcription factor-1 (TTF-1)

To evaluate the usefulness of thyroid transcription factor-1 (TTF-1) and CDX-2 in determining the primary tumor site of metastatic adenocarcinomas (ACs) in serous effusions cell blocks were constructed from cells in metastatic AC effusion fluids (n=97) that had been previously stained with a panel of antibodies against MOC-31, D2-40 and calretinin. Primary tumor sites included the lungs (n=52), ovaries (n=6), pancreas (n=4), breasts (n=3), bile duct (n=2) stomach (n=28) and colon (n=2). The lung ACs showed TTF-1 positivity in 58 percent (30/52) of cases. All nonpulmonary ACs lacked TTF-1 staining. All non-GI ACs lacked CDX-2 staining. Specificities and positive predictive values for TTF-1 and CDX-2 equaled 100 percent for metastatic pulmonary and GI ACs, respectively. The results suggested that TTF-1 and CDX-2 are specific markers to separate metastatic pulmonary and GI ACs, respectively, from other metastatic ACs in serous effusions. However, sensitivity values of these markers were low [458].

TP53

TP53 has a fundamental role in cell cycle and apoptosis and is frequently mutated in solid tumours, including pancreatic cancer. Based on the assumption that genetic variation may affect susceptibility to cancer development, the role of TP53 polymorphisms in modulating the risk of pancreatic cancer may be of major importance. It was investigated four selected polymorphisms in TP53 (rs17878362:A(1)>A(2), rs1042522:G>C, rs12947788:C>T and rs17884306:G>A) in association with pancreatic cancer risk in a case-control study, including 240 cases and controls (for a total of 1827 individuals) from the Czech Republic. Carriers of the variant C allele of rs1042522 polymorphism were at a significantly increased risk of pancreatic cancer (odds ratio 1.73; 95 % confidence interval 1.26 to 2.39). Haplotype analysis showed that in comparison with the most common haplotype (A(1)GCG), the A(2)CCG haplotype was associated with a significant increased risk (OR 1.39; 95 % confidence interval 1.02 to 1.88) and the A(1)CCG with a significantly reduced risk (OR 0.30; 95 % confidence interval 0.12 to 0.76) for this cancer. These results reflect previous findings of a recent association study, where haplotypes constructed on the same TP53 variants were associated with colorectal cancer risk [Polakova et al. Genotype and haplotype analysis of cell cycle genes in sporadic colorectal cancer in the Czech Republic. Hum. Mutat 2009; 30: 661-8]. Genetic variation in TP53 may contribute, alone or in concert with other risk factors, to modify the inherited susceptibility to pancreatic cancer, as well as to other gastrointestinal cancers [459].

Biology of metastases

Metastasis, the dissemination and growth of neoplastic cells in an organ distinct from that in which they originated, is the most common cause of death in cancer patients. This is particularly true for pancreatic cancers, where most patients are diagnosed with metastatic disease and few show a sustained response to chemotherapy or radiation therapy. Whether the dismal prognosis of patients with pancreatic cancer compared to patients with other types of cancer is a result of late diagnosis or early dissemination of disease to distant organs is not known. Here it was relied on data generated by sequencing the genomes of seven pancreatic cancer metastases to evaluate the clonal relationships among primary and metastatic cancers. It was found that clonal populations that give rise to distant metastases are represented within the primary carcinoma, but these clones are genetically evolved from the original parental, non-metastatic clone. Thus, genetic heterogeneity of metastases reflects that within the primary carcinoma. A quantitative analysis of the timing of the genetic evolution of pancreatic cancer was performed, indicating at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell. At least five more years are required for the acquisition of metastatic ability and patients die an average of two years thereafter. These data provide novel insights into the genetic features underlying pancreatic cancer progression and define a broad time window of opportunity for early detection to prevent deaths from metastatic disease [460].

Pancreatic cancer is an aggressive malignancy with a five-year mortality of 97-98 percent, usually due to widespread metastatic disease. Previous studies indicate that this disease has a complex genomic landscape, with frequent copy number changes and point mutations, but genomic rearrangements have not been characterized in detail. Despite the clinical importance of metastasis, there remain fundamental questions about the clonal structures of metastatic tumours, including phylogenetic relationships among metastases, the scale of ongoing parallel evolution in metastatic and primary sites, and how the tumour disseminates. Here it was harnessed advances in DNA sequencing to annotate genomic rearrangements in 13 patients with pancreatic cancer and explore clonal relationships among metastases. It was found that pancreatic cancer acquires rearrangements indicative of telomere dysfunction and abnormal cell-cycle control, namely dysregulated G1-to-S-phase transition with intact G2-M checkpoint. These initiate amplification of cancer genes and occur predominantly in early cancer development rather than the later stages of the disease. Genomic instability frequently persists after cancer dissemination, resulting in ongoing, parallel and even convergent evolution among different metastases. It was found evidence that there is genetic heterogeneity among metastasis-initiating cells, that seeding metastasis may require driver mutations beyond those required for primary tumours, and that phylogenetic trees across metastases show organ-specific branches. These data attest to the richness of genetic variation in cancer, brought about by the tandem forces of genomic instability and evolutionary selection [461].

Tumor metastasis is challenged by its resistance to microenvironmental stress infringed during escape from the primary tumor and the colonization of a foreign secondary tissue. Because of its great metastatic potential and its strong resistance to anticancer drugs, pancreatic cancer is regarded as a paradigm of the adaptation of cancer cells to microenvironmental stress. Thus, to understand how pancreatic cancer cells adapt to the different endogenous and therapy-related stresses is crucial for understanding their etiology and for the development of new efficient anticancer strategies. A review summarized the multiple functions accomplished by one major factor of pancreatic cancer cell stress response, the stress protein p8 [462].

Prognostic factors

Circulating endothelial cells

To evaluate circulating endothelial lineage cells (ELCs) as biomarkers of tumor neovascularization in patients with pancreatic ductal adenocarcinoma (PDAC) ELCs were isolated from the peripheral blood of patients with PDAC (n=14) or controls (n=17) before and after tumor resection and quantified using flow cytometry. Vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) were detected in tumor using immunohistochemistry and in plasma using an ELISA technique. Circulating ELC levels were increased in patients with PDAC compared to controls. After PDAC resection, ELC levels declined. ELC level increases were associated with cancer recurrence. VEGF and PIGF were identified in cancer cells and exocrine pancreas cells. Only PIGF was detected in tumor-associated inflammatory cells. Plasma levels of PIGF were higher in patients with PDAC compared to controls. It was concluded that circulating ELCs are a potential biomarker of PDAC neovascularization [463].

Ki-67

Morphometry – nuclear Ki-67 labelling, mitotic activity index (MI), and volume-corrected mitotic index (M/V) – for periampullary cancers using tissue microarrays has not been performed previously. The purpose of the study was to assess these indices on tissue microarray (TMA) sections constructed from patients with periampullary cancers and study their association with clinicopathological variables. Immunohistochemical staining for Ki-67 was performed on formalin-fixed pancreatic TMA sections. Expression of Ki-67 was assessed as the percentage of cancer cell nuclei expressing MIB1, MI as the mean percentage of Ki-67 from 10 random high-power fields, and M/V was calculated after standardizing MI for connective tissue volume and microscope parameters in the tumor using established protocols. Patients ≥ 70 years with periampullary cancers had higher Ki-67 expression (>15) compared with patients <70 years of age. Ki-67 expression was higher in tumors ≥ 2 cm compared with smaller tumors. Higher MI (>15) was clearly associated with worsening histological grade. The median survival for tumors of the pancreaticobiliary subtype (pancreatic ductal adenocarcinoma and cholangiocarcinoma) was 43 months in the group with an M/V score of <20 , compared with 18 months for the group with a score ≥ 20 . There was no statistically significant difference in survival, based on M/V score, for tumors of the intestinal subtype (ampullary and duodenal adenocarcinoma). In periampullary cancers, Ki-67 and MI are proliferative indices predictive of tumor behavior. M/V was predictive of survival in tumors of the pancreaticobiliary subtype [464].

Mucins

One study investigated the association of mucins and cluster of differentiation (CD) 56 with vascular and perineural invasion and survival in patients with periampullary cancer. Immunohistochemical staining was performed on formalin-fixed pancreatic tissue microarrays (cancer, chronic pancreatitis and normal pancreatic tissue) constructed from 126 pancreatic resections (cancer, 104; chronic pancreatitis, 22). Mucin (MUC) 1, MUC4 and MUC5AC expression was quantified using the immunohistochemical score (range 0-300), MUC3 expression was described as membranous or cytoplasmic, and expression of CD56, MUC2 and MUC6 as present or absent. In cancers, vascular invasion correlated significantly with overexpression (immunohistochemical score of 100 or more) of MUC1 and presence of MUC6, and perineural invasion correlated with overexpression of MUC5AC. Reduced survival was observed with overexpression of MUC4 and MUC5AC, membranous expression of MUC3, and presence of CD56. Perineural invasion also correlated with CD56 expression. Overexpression of MUC4 and MUC5AC correlated significantly with tumour recurrence.

Multivariable analysis identified membranous expression of MUC3, lymphatic invasion, and perineural invasion as significant independent predictors of poor survival [465].

Neutrophil-lymphocyte ratio

The objective of one study was to investigate whether the preoperative hematologic markers, the platelet-lymphocyte ratio (PLR), or the neutrophil-lymphocyte ratio (NLR) ratio are significant prognostic indicators in resected pancreatic ductal adenocarcinoma. A total of 84 patients undergoing pancreatoduodenectomy for pancreatic ductal adenocarcinoma over a 10-year period were identified from a retrospectively maintained database. The preoperative NLR was found to be a significant prognostic marker, whereas PLR had no significant relationship with survival using univariate Cox survival analysis. The median overall survival in patients with an NLR of ≤ 3.0 (n=55) was 14, 17 months in those with an NLR of 3.0 to 4.0 (n=17) and 6 months in patients with a value of >4.0 (n=12). The NLR retained its significance on multivariate analysis along with resection margin status. The preoperative neutrophil-lymphocyte ratio represents a significant independent prognostic indicator in patients with resected pancreatic ductal adenocarcinoma, whereas platelet-lymphocyte ratio does not [466].

Stromal cell-derived factor-1

Stromal cell-derived factor-1 (SDF-1) and its receptor, CXCR4, have been shown to mediate invasiveness and metastatic behavior in a number of cancers, including ovarian, prostate, bladder, breast, and pancreatic cancers. The expression and significance of SDF-1 in pancreatic ductal adenocarcinoma (PDA) have not been systematically studied. It was therefore examined the expression of SDF-1 by immunohistochemistry using a mouse anti-human SDF-1/CXCL12 antibody (dilution 1:300) and a tissue microarray consisting of 72 stage II PDAs from pancreaticoduodenectomy specimens. The staining results were categorized as SDF-1-high (SDF-1-H; cytoplasmic staining of $\geq 10\%$ of tumor cells) or SDF-1-low (SDF-1-L; no staining or staining of $<10\%$ of tumor cells). The results of SDF-1 expression were correlated with clinicopathologic parameters and survival. Of the 72 stage II PDAs, 25 (35 %) showed high levels of SDF-1 expression. The median overall and recurrence-free survival for patients with SDF-1-H PDAs were 26 and 11 months, respectively, compared with 44 and 22 months for patients with SDF-1-L tumor. In multivariate analysis, high SDF-1 expression correlated with poor overall and disease-free survival independent of tumor size, differentiation, and lymph node status. It was concluded that high levels of SDF-1 expression were associated with poor overall and disease-free survival in patients with stage II pancreatic adenocarcinoma [467].

Tumor markers

The performance of the 2 tumor markers carbohydrate antigen 19-9 (CA19-9) and tumor M2 pyruvate kinase (Tu-M2-PK) separately and in combination detecting pancreatic ductal adenocarcinoma was evaluated in a prospective study. The study comprised 103 patients referred because of suspicion of pancreatic cancer. Of these, 51 patients had their conditions diagnosed as pancreatic ductal adenocarcinoma, whereas this diagnosis was ruled out in 52 after 12 months of follow-up. The performance of Tu-M2-PK was compared with that of CA19-9 using cutoff values 15 and 37 U/mL, respectively. The sensitivity of Tu-M2-PK and CA19-9 in detecting PDAC was 55 percent and 86 percent at specificities of 52 percent and 73 percent, respectively. The area under the curve (AUC) of Tu-M2-PK was 0.55 and that of CA19-9 was 0.84. Combining the 2 markers did not significantly improve AUC (AUC = 0.85) compared with CA19-9 when used alone. The presence of chronic pancreatitis or jaundice causes increased levels of CA19-9 but does not influence Tu-M2-PK. It was concluded that Tu-M2-PK was inferior to CA19-9 as marker of PDAC. Tu-M2-PK may have a role in

diagnosing pancreatic ductal adenocarcinoma because it is not affected by cholestasis or Lewis phenotype. Neither tumor marker can stand alone in the diagnosis of PDAC [468].

The relationship between diabetes and pancreatic cancer has been established by more than several decades of research. However, serum levels of CEA and CA 19-9 in diabetic pancreatic cancer has not been investigated properly. Preoperative serum levels of CEA and CA 19-9 and clinicopathological characteristics were retrospectively analyzed in 79 with or 229 without diabetes in pancreatic ductal adenocarcinoma (PDA) patients. Of the 308 PDA patients enrolled, 79 (26 %) patients had diabetes. The percentage of new-onset diabetes (i.e. <24 months in duration) was 57 percent (45/79) in PDA patients coupled with diabetes. Among diabetic PDA patients, mean total bilirubin and fasting blood glucose significantly increased in comparison with control groups. No significant differences were observed in mean levels of serum CA 19-9 and CEA levels between two groups. However, when the value of CEA and CA 19-9 was analyzed as a dichotomous variable, elevated CEA (≥ 5 ng/ml) and CA 19-9 (≥ 500 U/ml) levels were strongly correlated with the presence of diabetes in PDA patients. It was concluded that elevated CEA (≥ 5 ng/ml) and CA19-9 (≥ 500 U/ml) levels have an association with diabetic pancreatic cancer. New-onset diabetes combined with higher CA 19-9 and/or CEA might be regarded as a useful tool to screen early pancreatic cancer [469].

Postoperative tumor markers

The purpose of one study was to obtain a comprehensive understanding of the impact of postoperative tumor marker (TM) normalization on survival after pancreatectomy for pancreatic carcinoma. It was proposed the concept of surgical RECIST based on residual tumor and TM status. A total of 194 consecutive patients with pancreatic carcinoma underwent pancreatectomy between 1989 and 2008. Postoperative TM levels remained elevated in 92 patients (47 %; partial responders). TM levels normalized in 102 patients (53 %; complete responders). Lymph node metastases, portal vein resection, absence of retroperitoneal clearance, residual tumor, preoperative high CA19-9, and surgical partial response were associated with decreased survival. Nodal stage and surgical RECIST were significant predictors of survival. Partial responders had a significantly lower median survival time and significantly higher frequency of hepatic metastasis. It was concluded that postresection tumor marker normalization is a strong prognostic factor for pancreatic cancer. The efficacy of pancreatic cancer surgery should be evaluated in the context of both local clearance and serum tumor marker kinetics [470].

CA 19-9

Serum carbohydrate antigen 19-9 (CA19-9) level has been reported to be a useful prognostic marker in pancreatic cancer. The purpose of this study was to determine which prognostic factor (preoperative or postoperative serum CA19-9 level) is more useful. Pre- and postoperative serum CA19-9 levels were measured in 109 patients who underwent surgical resection for pancreatic cancer between 1998 and 2009, and their relationships to clinicopathological factors and overall survival were analyzed with univariate and multivariate methods. In univariate analysis, tumor location, postoperative adjuvant chemotherapy, residual tumor factor status, UICC pT stage, lymph node metastasis, and UICC final stage were significantly associated with overall survival. Differences in overall survival were significant between groups divided on the basis of four postoperative CA19-9 cutoff values (37, 100, 200, and 500 U/ml) but not significant between groups divided on the basis of the same four preoperative CA19-9 cutoff values. Pre- to postoperative increase in CA19-9 level also was significantly associated with poor prognosis. In multivariate analysis, postoperative adjuvant chemotherapy (HR 1.59) and postoperative CA19-9 cutoff value of 37 U/mL (HR 1.64) remained independent predictors of prognosis. It was concluded that postoperative CA19-9 level is a better prognostic factor than preoperative CA19-9 level, and curative surgery for resectable pancreatic cancer should be tried regardless of the preoperative CA19-9 level [471].

Other biomarkers

Biomarkers that detect pancreatic cancer at earlier stages could improve the outcome of this deadly disease. It was investigated a dozen biomarker candidates for their potential as pancreatic cancer blood biomarkers using enzyme-linked immunosorbent assays. Among them, the macrophage migration inhibitory factor and osteopontin blood tests were nearly perfect in distinguishing pancreatic cancer cases from healthy controls (100 % and 95 % sensitivity, respectively, at 100 % specificity). Five biomarker candidates were then tested on an expanded set of diseased controls, which included sera from patients with pancreatitis. The sensitivity dropped significantly for all 5 candidate markers. The results suggest that biomarker candidates could fail in various steps of biomarker development. Earlier knowledge of candidate biomarker flaws could lead to strategies to overcome the flaw or alternatively lead to earlier termination of biomarkers that are prone to failure in the later phases of validation testing [472].

Metabolic profiling of biofluids is emerging as an important area with a promising number of applications in clinical medicine, including early diagnosis of numerous diseases that normally remain silent until late in the progress of disease. While blood and urine are more often used to explore biomarkers that distinguish the healthy from disease conditions, human bile is emerging as a rich source of biomarkers specifically for the cancers of the liver (hepatocellular carcinoma), bile ducts (cholangiocarcinoma), gallbladder and pancreas. This is owing to the fact that metabolites linked to the pathways of tumor cell metabolism are rich in bile by virtue of its association or proximity to the pathological source. Recent methodological developments have enabled the identification of a number of bile metabolites that have links with hepatopancreatobiliary diseases. Investigations of human bile are also considered to help the biomarker discovery process *in vitro* and provide avenues for translational research in detecting and following dynamic variations of biomarkers in clinical settings using noninvasive approaches, such as *in vivo* magnetic resonance spectroscopy. One article reviewed the current status and potential applications of human bile as a source of biomarkers, with emphasis on metabolites, for early detection of cancers associated with the hepatopancreatobiliary system [473].

Pancreatic cancer is an aggressive tumour following a multistep progression model through precursors called pancreatic intraepithelial neoplasia (PanIN). Identification of reliable prognostic markers would help in improving survival. The aim of one study was to investigate the role as well as the prognostic significance of different cell cycle and proliferation markers, namely p21, p27, p53 and Ki-67, in pancreatic carcinogenesis. It was analysed the expression of p21, p27, p53 and Ki-67, in 210 ductal pancreatic adenocarcinomas, 40 PanIN-3 cases and 40 normal controls combined in a tissue microarray. The results were correlated with clinicopathological and follow-up data. The study revealed a differential p27, p21, p53, and Ki-67 expression between ductal adenocarcinoma, PanIN-3 and normal pancreas. p27 expression progressively decreased from normal pancreas to PanIN and to pancreatic cancer. Decreased p27 and increased p53 expression showed a significant association with the T stage. A Ki-67 >5% correlated with reduced survival. It was concluded that in pancreatic cancer, loss of p27 and increased p53 expression is associated with a more aggressive phenotype. p27 may play an important role in pancreatic carcinogenesis. A Ki-67 >5% independently predicted poor outcome [474].

Cell-cell adhesion is a major factor in integrity of epithelia which is frequently disturbed in cancer leading to local invasion and distant metastasis. To define expression and function of activated leukocyte cell adhesion molecule (ALCAM, CD166) in pancreatic cancer and in pancreatic neuroendocrine tumors (PNET), microarray analyses, RT-PCR, immunohistochemistry, RNAi, adhesion, migration, invasion, and chemoresistance assays were used. It

was demonstrate that expression of ALCAM is altered and its serum levels are increased in pancreatic ductal adenocarcinoma (PDAC). ALCAM was expressed on the membranes of islet cells in the normal pancreas whereas normal pancreatic ducts were ALCAM-negative. In PDAC, ALCAM expression was generally rare though in some tumors, membranous, or cytoplasmic ALCAM was found. PNET were mostly ALCAM-positive with a cytoplasmic staining pattern which was in contrast to the membrane expression observed in non-transformed islet cells. In vitro, ALCAM silencing using RNAi had no effects on growth or invasion of pancreatic cancer cells but reduced cell adhesion and induced chemoresistance. In neuroendocrine tumor cell lines, silencing of ALCAM decreased cell growth. It was propose ALCAM as a novel serum biomarker in human pancreatic tumors which is associated with cell adhesion, growth and chemoresistance [475].

Biomarkers that detect pancreatic cancer at earlier stages may improve the outcome of this deadly disease. It was investigated a dozen biomarker candidates for their potential as pancreatic cancer blood biomarkers using enzyme-linked immunosorbent assays. Among them, the macrophage migration inhibitory factor and osteopontin blood tests were nearly perfect in distinguishing pancreatic cancer cases from healthy controls (100 % and 95 % sensitivity, respectively, at 100% specificity). Five biomarker candidates were then tested on an expanded set of diseased controls, which included sera from patients with pancreatitis. The sensitivity dropped significantly for all 5 candidate markers. The results suggest that biomarker candidates could fail in various steps of biomarker development. Earlier knowledge of candidate biomarker flaws could lead to strategies to overcome the flaw or alternatively lead to earlier termination of biomarkers that are prone to failure in the later phases of validation testing [476].

Fine needle aspiration biopsy

The aim of one study was to determine whether the presence of a biliary stent during endoscopic ultrasound fine-needle aspiration (EUS-FNA) affects diagnosis and complication rates. A retrospective analysis was performed of 268 patients with pancreatic head or neck adenocarcinoma who underwent EUS-FNA at an academic medical center between 2000 and 2009. Endoscopic ultrasound fine-needle aspiration and endoscopic retrograde cholangiopancreatography reports, cytology results, and physicians' notes were reviewed. A total of 170 patients without stents, 87 patients with stents placed more than 1 day before EUS, and 11 patients with stents placed less than 1 day before EUS were identified. In patients without stents, the tissue diagnosis rate via EUS-FNA was 92 percent compared with a rate of 89 percent for those with stents placed more than 1 day before EUS-FNA. However, the patients with stents placed immediately before EUS-FNA were significantly more likely to have indeterminate results from the EUS-FNA than the other patients were. Complication rates were the same among the groups. It was concluded that pre-EUS stenting of biliary obstruction due to pancreatic adenocarcinoma does not influence the rate of tissue diagnosis if performed more than 1 day before EUS-FNA. Lack of immediate EUS access should not preclude stent placement in appropriate patients with malignant biliary obstruction who will undergo EUS-FNA [477].

Brush cytology

Pancreatobiliary malignancies often present as biliary strictures. Biliary brush cytology is an established diagnostic technique in the investigation of such strictures. The main shortcoming of the test, however, is its low sensitivity. The aim of one study was to identify factors associated with a positive yield on biliary brush cytology. Consecutive patients who had brush cytology for investigation of biliary strictures from 2005 to 2007 were included. Association of several factors with a positive result on brush cytology was studied using univariable and multivariable logistic regression analyses. Two hundred eighty patients were evaluated. One hundred nineteen (43 %) patients had a final diagnosis of malignancy; of whom, 55 had a positive brush cytology (sensitivity, 46 %; specificity, 100 %). On multivariable analysis, age (odds ratio, 1.2; 95 % confidence interval 1.06 to 10.4 per 5-year

increase), total serum bilirubin levels (OR, 1.3; 95 % confidence interval, 1.01 to 1.6 per 5-unit increase), and presence of a mass on cross-sectional imaging (OR, 11.7; 95 % confidence interval 5.1 to 27.2) were independent predictors of a positive brush cytology result. It was concluded that increasing age, higher serumbilirubin levels, and presence of a mass on cross-sectional imaging are independent factors associated with a positive result on biliary brush cytology. These findings suggest use of complementary tissue acquisition techniques in selected cases [478].

Elastography

Qualitative endoscopic ultrasound (EUS) elastography is an accurate but subjective tool for the differential diagnosis of solid pancreatic masses. Second-generation EUS elastography allows quantitative analysis of tissue stiffness. It was evaluated the accuracy of quantitative, second-generation EUS elastography in the differential diagnosis of solid pancreatic masses. The study included 86 consecutive patients who underwent EUS for the evaluation of solid pancreatic masses. EUS elastography was performed with the linear Pentax EUS and the Hitachi EUB900. Representative areas from the mass (A) and soft reference areas (B) were analyzed. The result of the elastographic evaluation was defined by the quotient B/A (strain ratio). Final diagnosis was based on histology of surgical specimens and cytology of EUS-fine-needle aspiration samples. The diagnostic accuracy of EUS elastography in detecting malignancy was calculated using receiver operating curve analysis. The mean size of the pancreatic masses was 31 mm. The final diagnoses were pancreatic adenocarcinoma (n=49), inflammatory mass (n=27), malignant neuroendocrine tumor (n=6), metastatic oat-cell lung cancer (n=2), pancreatic lymphoma (n=1), and pancreatic solid pseudopapillary tumor (n=1). The strain ratio was significantly higher among patients with pancreatic malignant tumors compared with those with inflammatory masses. The sensitivity and specificity of strain ratio for detecting pancreatic malignancies were 100 percent and 93 percent, respectively (area under the receiver operating curve, 0.983). It was concluded that quantitative, second-generation EUS elastography is useful for differential diagnosis of solid pancreatic masses. It allows for a quantitative and objective evaluation of tissue stiffness, which indicates the malignant or benign nature of the pancreatic lesion [479].

Histopathology

Entirely new TNM classifications in 2010 are those for gastrointestinal stromal tumours, gastrointestinal neuroendocrine tumours, intrahepatic cholangiocarcinoma and perihilar extrahepatic bile duct carcinomas. Major and praxis-relevant alterations concern colorectal tumours and include new classifications of carcinomas and carcinoids of the appendix. Minor alterations are seen in the classification of hepatocellular carcinomas. No changes were made for tumours of the anal canal, the gallbladder (excluding the inclusion of tumours of the cystic duct) and tumours of the pancreas and the ampulla of Vater [480].

Stromal cells are a functionally important component of human carcinomas. The aim of one study was to obtain and characterise primary cultures of stromal cells from human carcinomas and the corresponding surrounding normal tissue. Primary stromal cell cultures from tumours of lung, esophagus and pancreas were obtained using a mild tissue dissociation method and a medium for culturing mesenchymal cells. Immunofluorescence staining and western blotting were used to analyse the expression of differentiation markers and selected known oncoproteins in the cell cultures obtained. A panel of stromal primary cultures was prepared from different human tumours and from matched normal cancer-free tissues. The in vitro proliferative potential of tumour-associated fibroblasts was shown to be higher than that of matched normal stromal cells. A mutational analysis of the TP53 and KRAS2 genes in a number of stromal cultures did not reveal known mutations in most cells of the cultures studied. Western blot analysis showed that stromal cells of lung tumors were characterised by a statistically significantly lower expression level of the p16 protein as

compared with that in normal lung stromal cells. An important finding of the study was that, according to immunofluorescence assay, a fraction of fibroblast-like vimentin-positive cells in some tumour and normal stromal cell cultures expressed epithelial marker, cytokeratins. It was concluded that proliferating stromal cells from the carcinomas studied proved to be genetically normal cells with altered expression profiles of some genes involved in carcinogenesis, as compared with normal stromal cells. Epithelial-mesenchymal transition may lead to the emergence of transdifferentiated fibroblast-like cells in tumour stroma and in the tumor-surrounding tissue [481].

The aim of one study was to develop a method of gross examination of pancreaticoduodenectomy specimens with pancreatic ductal adenocarcinoma, allowing adequate assessment of the entire pancreatic surface as a surgical margin, which would not affect the lymph node yield. It was retrospectively compared the R1 rates (i.e. proportions of patients with microscopic residual tumour at surgical margins) and lymph node yield in a series of 67 consecutive cases of pT3 ductal adenocarcinomas diagnosed in pancreaticoduodenectomy specimens during three different periods of time and sampled using three different approaches:

- period 2006-2007, when the pancreatic surface (except for the transection margin and superior mesenteric artery margin) was not examined
- period January to September 2008, when the posterior pancreatic surface (posterior circumferential radial margin) was examined using an improved method based on sampling of 2.0-2.5 mm thick consecutive slices perpendicular to the duodenal axis
- period October 2008 to June 2009, when the whole surface of the pancreatic head was sampled using the approach mentioned above.

The R1 rates in three consecutive time periods were 24 percent, 40 percent and 54 percent, respectively. Median numbers of retrieved peripancreatic lymph nodes were 11, 12 and 14, respectively. It was concluded that the newly proposed approach allowed adequate assessment of the entire pancreatic head surface as a surgical margin and reduced the risk of under-detection of R1 status. Moreover, this approach did not affect the number of peripancreatic lymph nodes examined [482].

A wide variety of intratumor glandular differentiation, including solitary infiltrating cancer cells, is a prominent microscopic finding in pancreatic cancer. It was reviewed 114 resected cases of pancreatic ductal adenocarcinoma to investigate the prognostic impact of the degree of solitary cell infiltration, defined by the number of solitary infiltrating cancer cells. The clinicopathologic correlation of solitary cell infiltration was further evaluated. Seventy-six (67 %) cases showed 7 or more solitary infiltrating cancer cells in 10 high-power fields and were labeled as having a high degree of solitary cell infiltration. A high degree of solitary cell infiltration correlated significantly with poor overall survival, the grade, lymphatic invasion, and lymph node metastasis. Multivariate analysis revealed that the degree of solitary cell infiltration, the grade, and the margin status were independent prognostic factors. Grade 1 and 2 tumors with a high degree of solitary cell infiltration, compared with low infiltration, correlated significantly with poor overall survival. Grade 3 tumors showed a worse overall survival than grade 1 and 2 tumors with either a high or a low degree of solitary cell infiltration. Immunohistochemical analysis showed that a high degree of solitary cell infiltration correlated with reduced E-cadherin and increased vimentin expression. In conclusion, solitary cell infiltration is a significant prognostic indicator and serves as a morphological clue to epithelial-mesenchymal transition in pancreatic cancer [483].

Micrometastases

The clinical significance of micrometastasis to regional lymph nodes for pancreas cancer is controversial in patients who underwent curative resection. Nine of 42 patients who underwent macroscopically curative resection of pancreatic head cancer were found to have pN(-) by routine examination. Complete serial section examination of the resected specimens was done to detect micrometastasis in these 9 patients. A total of 16,505 sections were examined by immunohistochemistry or hematoxylin and eosin staining. Micrometastases were identified in 7 (78 %) of 9 patients and 17 (4 %) of 474 lymph nodes. All micrometastases were found in the pancreas head area. However, the frequency of micrometastases around the superior mesenteric artery was 44 percent. There were no micrometastases to the para-aortic nodes. There was a tendency that the patients with micrometastases showed better survival than those with overt nodal involvement. Micrometastasis did not provide the poor prognostic factor in patients who underwent optimal regional lymphadenectomy. It was concluded that even in overtly pN(-) pancreatic cancer, micrometastases occur high frequently (78 %) and widely, including the nodes around the superior mesenteric artery. These results provide important pathological information to be considered in preoperative, perioperative, and postoperative strategies, even when patients seem to have no nodal involvement by preoperative examinations [484].

Lymphangiogenesis

The aim of one study was to investigate the significance of lymphangiogenesis in primary pancreatic tumors and in draining lymph nodes during lymphatic metastasis of pancreatic head cancers. Specimens were obtained from 70 patients. To evaluate lymphangiogenesis, we measured lymphatic vessel density (LVD) using D2-40 antibody in the primary tumors and in the draining lymph nodes. AE1/AE3 antibody was used to detect tiny, histologically negative metastases in lymph nodes. Patients with high LVD of primary tumors had significantly higher incidence of node metastasis and lower postoperative survival rate than those with low LVD. Intranodal LVDs increased with increasing size of the intranodal metastases. The LVDs of non-metastatic nodes in patients with node metastasis were also significantly higher than those of non-metastatic nodes in patients without node metastasis. The LVDs of peripancreatic nodes in patients with paraaortic node metastases were significantly higher than those in patients without paraaortic metastasis. It was concluded that lymphangiogenesis in primary tumors and draining lymph nodes is essential for efficient spread of tumor cells through the lymphatic system [485].

Lymph nodes

Preoperative lymph node staging of pancreatic cancer by CT relies on the premise that malignant lymph nodes are larger than benign nodes. In imaging procedures lymph nodes >1 cm in size are regarded as metastatic nodes. The extent of lymphadenectomy and potential application of neoadjuvant therapy regimens could be dependent on this evaluation. In a morphometric study regional lymph nodes from 52 patients with pancreatic cancer were analyzed. The lymph nodes were counted, the largest diameter of each node was measured, and each node was analyzed for metastatic involvement by histopathological examination. The frequency of metastatic involvement was calculated and correlated with lymph node size. A total of 636 lymph nodes were present in the 52 specimens examined for this study (12 lymph nodes per patient). Eleven patients had a pN0 status, whereas 41 patients had lymph nodes that were positive for cancer. Five-hundred-twenty (82 %) lymph nodes were tumor-free, while 116 (18 %) showed metastatic involvement on histopathologic examination. The mean diameter of the nonmetastatic nodes was 4.3 mm, whereas infiltrated nodes had a diameter of 5.7 mm, which was a significant difference. Seventy-eight (67 %) of the infiltrated lymph nodes and 433 (83 %) of the nonmetastatic nodes were ≤5 mm in diameter. Of 11 pN0

patients, 5 (45 %) patients had at least one lymph node ≥ 10 mm, in contrast only 12 (29 %) out of 41 pN1 patients had one lymph node ≥ 10 mm. It was concluded – again – that lymph node size is not a reliable parameter for the evaluation of metastatic involvement in patients with pancreatic cancer [486].

Influence of grade

AJCC staging of pancreatic cancer (PAC) is used to determine prognosis, yet survival within each stage shows wide variation and remains unpredictable. It was hypothesized that tumor grade might be responsible for some of this variation and that the addition of grade to current AJCC staging would provide improved prognostication. The Surveillance, Epidemiology, and End Results (SEER) database (1991-2005) was used to identify 8082 patients with resected PAC. Patients who did not undergo cancer-directed surgery were excluded from the analysis. Also excluded were patients with no histological confirmation of the diagnosis and cases identified from autopsy reports only. Complete TNM data were available for 7627 out of 8082 patients (94 %). In the SEER database, tumor grade is coded as 1 (well differentiated), 2 (moderately differentiated), 3 (poorly differentiated), or 4 (undifferentiated). Tumor grade was recorded for 7086 out of 8082 patients (88 %). The impact of grade on overall and stage-specific survival was assessed using Cox regression analysis. Variables in the model were age, sex, tumor size, lymph node status, and tumor grade. For each AJCC stage, survival was significantly worse for high-grade versus low-grade tumors. Multivariate analysis of the entire cohort identified the following independent predictors of adverse outcome: increasing age, male sex, tumor size > 2 cm, lymph node positivity, and high tumor grade. Importantly, the hazard ratio (HR) associated with high tumor grade (HR 1.4) was of a similar magnitude and significance when compared with tumor size (HR 1.37) and node status (HR 1.38). Also on multivariate analysis, high tumor grade was an independent predictor of survival for the entire cohort (hazard ratio 1.40, 95 % confidence interval 1.31 to 1.48) as well as for stage I (HR 1.28, 95 % confidence interval 1.07 to 1.54), stage IIA (HR 1.43, 95 % confidence interval 1.26 to 1.61), stage IIB (HR 1.38, 95 % confidence interval 1.27 to 1.50), stage III (HR 1.28, 95 % confidence interval 1.02 to 1.59), and stage IV (HR 1.58, 95 % confidence interval 1.21 to 2.05) patients. Interestingly, in the stage IV patients who underwent a resection, grade was the only independent prognostic variable (HR 1.58). The addition of grade to staging results in a statistically significant survival discrimination between all stages. It was concluded that tumor grade is an important prognostic variable of survival in pancreatic adenocarcinoma. It was proposed a novel staging system incorporating grade into current AJCC staging for pancreas cancer. It was shown that stratifying AJCC stage IIB resected tumors (node positive) by grade demonstrates a 4-month improvement in median survival for node-positive, low-grade tumors compared with node-positive, high-grade tumors, which is comparable to the difference in median survival seen in the trial results quoted previously. It may be possible to identify the “bad actors” in stage IIA (high-grade tumors, node negative, and locally invasive) and move them to stage IIB in TNMG staging; again an improvement in median survival of 2 months compared with stage IIA in TNM staging. Furthermore, dividing stage IV patients into stage IVA (low grade with median survival 8 months) and stage IVB (high grade with median survival 5 months) provides better risk stratification in the very patient population most likely to enroll in future clinical trials to evaluate potential new therapies. Moreover, in support of the contention that discrimination in survival is improved with TNMG staging, the overall “spread” in median survival for TNMG staging is 25 months (range 5-30 months), which compares with 21 months with TNM staging (range 6-27 months). The improved prognostication aimed to be more reflective of tumor biology and may impact therapy decisions and stratification of future clinical trials [487].

Nerve invasion

The ability of cancer to infiltrate along nerves is a common clinical observation in pancreas, head and neck, prostate, breast, and gastrointestinal carcinomas. For these tumors, nerves may provide a conduit for local cancer progression into the central nervous system. Although neural invasion is associated with poor outcome, the mechanism that triggers it is unknown. It was used an in vitro Matrigel dorsal root ganglion and pancreatic cancer cell coculture model to assess the dynamic interactions between nerves and cancer cell migration and the role of glial cell-derived neurotrophic factor (GDNF). An in vivo murine sciatic nerve model was used to study how nerve invasion affects sciatic nerve function. Nerves induced a polarized neurotrophic migration of cancer cells (PNMCs) along their axons, which was more efficient than in the absence of nerves. PNMC was induced by secretion of GDNF, via phosphorylation of the RET-Ras-mitogen-activated protein kinase pathway. Nerves from mice deficient in GDNF had reduced ability to attract cancer cells. Tumor specimens excised from patients with neuroinvasive pancreatic carcinoma had higher expression of the GDNF receptors RET and GRFalpha1 as compared with normal tissue. Finally, systemic therapy with pyrazolopyrimidine-1, a tyrosine kinase inhibitor targeting the RET pathway, suppressed nerve invasion toward the spinal cord and prevented paralysis in mice. The authors concluded that these data provide evidence for paracrine regulation of pancreatic cancer invasion by nerves, which may have important implications for potential therapy directed against nerve invasion by cancer [488].

To elucidate poorly understood pancreatic neural changes after upper abdominal surgery. It was histologically examined 57 postmortem pancreases after gastrectomy, esophagectomy, and esophageal transection, and also investigated each clinical manifestation. Six pancreases (11 %) had unique histopathological lesions composed of prominently thickened and/or proliferated neural fascicles. They focally or multifocally involved the pancreatic lobules and/or interlobular septa and mimicked traumatic neuroma. Three of the six lesions were accompanied by moderate to severe chronic pancreatitis/pancreatic fibrosis. All six patients were asymptomatic, although only one exhibited a low-echoic pancreatic mass. There were no statistically significant associations between the pancreatic neural lesions and the patients' sex, age, the time interval between the surgery and the patients' death, impaired glucose tolerance, the presence of hyalinized pancreatic islets, or the presence of moderate to severe chronic pancreatitis/pancreatic fibrosis. No similar prominent neural lesions were identified in an additional 57 age- and sex-matched control pancreases. It was concluded that these prominent neural lesions were pancreatic neuroma-like lesions following upper abdominal surgery. The study failed to demonstrate the distinct pathogenesis of the neuroma-like lesions and further investigation may be needed. However, this report is the first to delineate that asymptomatic neuroma-like lesions can occur following upper abdominal surgery [489].

Cytopathology

Endoscopic ultrasound-directed fine-needle aspiration is a minimally invasive technique for the biopsy of pancreatic cysts and mass lesions. The technique is associated with low morbidity and high diagnostic accuracy. Interpretation of cytologic material obtained from the pancreas is complex because of the large number of reactive processes and benign and malignant neoplasms arising within the pancreas. The cytologic appearances of a majority of pancreatic neoplasms are characteristic, allowing precise recognition of the type of neoplasm present. Whereas separation of neuroendocrine, acinar, and ductal neoplasms is usually straightforward, the greatest diagnostic challenge in pancreatic fine-needle aspiration is the separation of atypical epithelium secondary to chronic pancreatitis from well-differentiated ductal adenocarcinoma. Recently, a number of in situ lesions have been identified, complicating the cytologic diagnosis of pancreatic neoplasia. These noninvasive lesions

include pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm [490].

Tumors with cribriform nests

Pancreatic ductal adenocarcinoma (PDCA) is characterized by well-defined tubular units in the vast majority of the cases; however, variations in this theme do occur. It is important to recognize the morphologic spectrum of PDCA to avoid misdiagnosis especially in small specimens and also in metastatic foci. It was documented a morphologic variant of PDCA that is characterized by a distinctive pattern of infiltrating cribriform nests in a distinctive "microcystic" or "secretory" pattern. Twenty-four cases of PDCA have been identified in a review of 505 cases diagnosed with PDCA. Histologically, this pattern was characterized by infiltrating nests of tumor cells with large vacuoles and "signet-ring" like appearance imparting a cribriform growth pattern. The vacuoles were one to five cells in size, often merging to form multilocular spaces separated by a thin rim of cell membrane. Many of these spaces contained CA19-9 positive granular secretory material. The nuclei were often pushed to the periphery and compressed in a pattern resembling adipocytes, although the nuclei were often densely hyperchromatic and displayed significant atypia. Especially in biopsies from the peripancreatic fat and peritoneum, these neoplastic cells had been misdiagnosed as degenerating adipocytes, and in the lymph nodes, they had been misinterpreted as lipogranulomas. Clinical findings of the patients were similar to that of conventional PDCA, except a significantly higher incidence of history of smoking (83 % vs 60 %). In conclusion, vacuolated cell adenocarcinoma is a distinct morphologic variant of PDCA, and the presence of this peculiar pattern in a metastatic site, although not specific, should raise the suspicion of a PDCA [491].

Intratumoral cystic lesions

The purpose of one study was to evaluate intratumoral cystic lesions of pancreatic ductal adenocarcinoma (PDAC) depicted on MRI, and to correlate these cystic lesions with their histopathological findings. This study included 12 patients (7 males and 5 females; mean age, 59 years) with intratumoral cystic lesions of PDAC detected on a retrospective MRI review. It was reviewed the histopathological findings of the cystic lesions within PDACs and analysed the MRI findings, focusing on the appearance of the intratumoral cystic lesions, i.e. the size, number, margin and intratumoral location, and on the ancillary findings of PDAC, i.e. peripancreatic infiltration, upstream pancreatic duct dilatation and distal parenchymal atrophy. Intratumoral cystic lesions were classified as neoplastic mucin cysts (n=7) or cystic necrosis (n=5) according to the histopathological findings; they ranged in greatest dimension from 0.5 cm to 3.4 cm (mean, 1.7 cm). Seven patients had only one cystic lesion each, while the remaining five had multiple cystic lesions. Most of the neoplastic mucin cysts had smooth margins (86 %) and eccentric locations (n=6), whereas most cystic necroses had irregular margins (80 %) and centric locations (n=4). The most common ancillary findings of PDAC were peripancreatic infiltration, distal pancreatic atrophy and upstream pancreatic duct dilatation (92 %, 75 % and 58 %, respectively). The intratumoral cystic lesions of PDACs on MRI were classified as either neoplastic mucin cysts with smooth margins and eccentric locations or cystic necroses with irregular margins and centric locations [492].

Necrotic tumor tissue

Tumour necrosis reflects the presence of hypoxia, which can be indicative of an aggressive tumour phenotype. The aim of one study was to investigate whether histological necrosis is a useful predictor of outcome in patients with pancreatic ductal carcinoma (PDC). It was reviewed histopathological findings in 348 cases of PDC in comparison with clinic-pathological information. It was counted small necrotic foci (micronecrosis) as necrosis, in

addition to massive necrosis that had been only defined as necrosis in previous studies. The reproducibility of identifying histological parameters was tested by asking five independent observers to blindly review 51 examples of PDC. Both micronecrosis and massive necrosis corresponded to hypoxic foci expressing carbonic anhydrase IX detected by immunohistochemistry. Multivariate survival analysis showed that histological necrosis was an independent predictor of poor outcome in terms of both disease-free survival (DFS) and disease-specific survival (DSS) of PDC patients. In addition, metastatic status, and lymphatic, venous, and intrapancreatic neural invasion were independent prognostic factors for shorter DFS and metastatic status, margin status, lymphatic invasion, and intrapancreatic neural invasion were independent prognostic factors for DSS. The interobserver reproducibility of necrosis identification among the five independent observers was almost perfect. It was concluded that histological necrosis is a simple, accurate, and reproducible predictor of postoperative outcome in PDC patients [493].

Biobanking

Clinically annotated pancreatic cancer samples are needed for progress to be made toward developing more effective treatments for this deadly cancer. As part of a National Cancer Institute-funded program project, it was established a biospecimen core to support the research efforts. One article summarized the key hurdles encountered and solutions we found in the process of developing a successful multi-institution biospecimen repository [494].

Premalignancy

A 60-year-old man had an ERCP that showed stenosis of the main pancreatic duct at the junction of the pancreatic head and body. Brush cytology revealed pancreatic ductal carcinoma. Histological examination of the resected pancreas showed a 15-mm in length intraductal growth of carcinoma in situ in the main pancreatic duct, 10 mm of which showed microinvasion. There was also atypical hyperplasia at a branch pancreatic duct near the lesion. It was suspected to be an initial stage of pancreatic ductal carcinoma. Intraductal progression type and non-progression type are often suspected in a case showing progression of carcinoma in situ to pancreatic ductal carcinoma, and this case was thought to be intraductal progression [495].

PanINs

Pancreatic intraepithelial neoplasias (PanIN) are pancreatic cancer precursor lesions of unclear origin and significance. PanIN aberrantly express sonic hedgehog (Shh), an initiator of pancreatic cancer, and gastrointestinal mucins. A majority of PanIN are thought to arise from ducts. It was identified a novel ductal compartment that is gathered in gland-like outpouches (pancreatic duct glands, PDGs) of major ducts and characterized its role in injury and metaplasia. The ductal system was analyzed in normal pancreata and chronic pancreatitis in humans and mice. Anatomy was assessed by serial hematoxylin and eosin sections and scanning electron microscopy of corrosion casts. Expression of mucins and developmental genes and proliferation were assessed by immunohistochemistry or real-time quantitative polymerase chain reaction. Effects of Shh on ductal cells were investigated by exposure to Shh in vitro and transgenic misexpression in vivo. Three-dimensional analysis revealed blind-ending outpouches of ducts in murine and human pancreata. These PDG are morphologically and molecularly distinct from normal ducts; even in normal pancreata they display PanIN and metaplastic features, such as expression of Shh and gastric mucins. They express other developmental genes, such as Pdx-1 and Hes-1. In injury, Shh is up-regulated along with gastric mucins. Expansion of the PDG compartment results in a mucinous

metaplasia. Shh promotes this transformation in vitro and in vivo. PDG are distinct gland-like mucinous compartments with a distinct molecular signature. In response to injury, PDG undergo a Shh-mediated mucinous gastrointestinal metaplasia with PanIN-like features. PDG may provide a link between Shh, mucinous metaplasia, and neoplasia [496].

Pancreatic intraepithelial neoplasia (PanIN) has been found in association with pancreatic ductal adenocarcinoma, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystic neoplasm, and other pancreatic lesions, but the characteristics of PanINs associated with these lesions are not well characterized. In one study, 185 partial or total pancreatectomy specimens were collected, and 173 had complete slides for reviewed, which included 74 pancreatic ductal adenocarcinomas, 28 IPMNs, 7 mucinous cystic neoplasms, 44 other nonductal tumors, and 20 nontumorous lesions. Differences in grade, extent, and duct involvement among PanINs associated with different lesions were analyzed. Patients with PanINs were older than those without, regardless of associated tumor or lesions. No sex predilection was noted. PanINs were found in 89 percent, 96 percent, 86 percent, 64 percent, and 55 percent of pancreata with ductal adenocarcinomas, IPMNs, mucinous cystic neoplasm, other nonductal tumors, and nontumorous lesions, respectively. PanIN 1 and 2 were commonly associated with all types of lesions, but high-grade PanIN 3 was more frequently associated with ductal adenocarcinomas. Ductal involvement of PanINs was more extensive in association with ductal adenocarcinomas than in any other types of pancreatic tumors or lesions. PanINs associated with pancreatic ductal adenocarcinomas affected both the main and branched ducts, whereas PanINs associated with other types of pancreatic tumors or lesions were mainly present in the branch ducts. No statistical differences were observed in distribution, extent, and grade of PanINs among IPMNs, mucinous cystic neoplasms, other nonductal tumors, and nontumorous lesions. The study demonstrated a high concurrence between PanINs and other precancerous lesions and histologic features of PanINs associated with different pancreatic diseases [497].

Biliary intraepithelial neoplasia

Biliary intraepithelial neoplasia (BillIN), a preneoplastic condition that may precede invasive intrahepatic cholangiocarcinoma (ICC), has been compared to pancreatic intraepithelial neoplasia (PanIN), a precursor lesion of pancreatic carcinoma. Biliary tract carcinoma development and progression is associated with several gene alterations, but BillIN lesions have yet to be studied in detail by molecular techniques. It was describe a case of extensive intrahepatic biliary dysplasia, with lesions ranging from BillIN-1 to BillIN-3 lesions, and multifocal microscopic ICC in hepatitis C virus (HCV)- and alcohol-related cirrhosis. The small ICC foci had remained undetected prior to transplantation. Fluorescence in situ hybridization (FISH) analysis was performed on three foci of BillIN-3 lesions and on three microinvasive ICC foci with a combination of three FISH probes directed against genes frequently altered in pancreatic and biliary tract carcinomas. FISH analysis revealed a CDKNA2 heterozygous deletion in one BillIN-3 focus, and in one non-contiguous ICC focus, although the deletion was just above the chosen threshold. No deletions were detected in the genomic regions encoding TP53 and SMAD4. This report documents for the first time the development of multifocal ICC in the setting of extensive biliary dysplasia in a patient with three risk factors, HCV infection, alcohol abuse, and cirrhosis, and suggests heterogeneous carcinogenesis in ICC and possible involvement of the CDKNA2 gene [498].

Experimental

Pancreatic intraepithelial neoplasia is a precursor to ductal adenocarcinoma of the pancreas that shows gastric differentiation. Pancreatic intraepithelial neoplasia-3 has the highest potential to progress to adenocarcinoma, and its distinction from lower-grade pancreatic intraepithelial neoplasias is important for clinical management. However, morphologic

grading of pancreatic intraepithelial neoplasia suffers from significant interobserver variability. A product of cell polarity gene lethal giant larvae 2 is a marker of gastric foveolar epithelium expressed in a basolateral fashion, which is lost or mislocalized in gastric epithelial dysplasia and adenocarcinoma. In one study, this was investigated a role of lethal giant larvae 2 expression in differentiating low-grade pancreatic intraepithelial neoplasias, that is, pancreatic intraepithelial neoplasia-1 and pancreatic intraepithelial neoplasia-2, from pancreatic intraepithelial neoplasia-3 and pancreatic ductal adenocarcinoma. The immunohistochemical patterns of lethal giant larvae 2 expression were examined in normal pancreatic ducts, 48 pancreatic intraepithelial neoplasia lesions of all histologic grades, and 91 adenocarcinomas on a tissue microarray or conventional sections. The expression pattern was recorded as basolateral, cytoplasmic, negative, or combinations of any of them. Whereas normal duct epithelia did not exhibit lethal giant larvae immunoreactivity, all but one lesion of low-grade pancreatic intraepithelial neoplasia showed basolateral lethal giant larvae staining. Conversely, all lesions of pancreatic intraepithelial neoplasia-3 and adenocarcinoma showed loss of lethal giant larvae 2 staining and/or its cytoplasmic localization. Interestingly, a basolateral expression was focally seen in 4 adenocarcinomas with a foamy gland pattern and was always admixed with negatively stained areas. In conclusion, the results show that low-grade pancreatic intraepithelial neoplasias express lethal giant larvae 2 in a basolateral fashion recapitulating expression in normal gastric epithelium. Loss or abnormal lethal giant larvae 2 expression is seen in pancreatic intraepithelial neoplasia-3 and adenocarcinoma and might be useful in separating them from lower-grade pancreatic intraepithelial neoplasias [499].

Early detection of pancreatic cancer

Lack of detection technology for early pancreatic cancer invariably leads to a typical clinical presentation of incurable disease at initial diagnosis. New strategies and biomarkers for early detection are sorely needed. In one study, it was conducted a prospective sample collection and retrospective blinded validation to evaluate the performance and translational utilities of salivary transcriptomic biomarkers for the noninvasive detection of resectable pancreatic cancer. The Affymetrix HG U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA) was used to profile transcriptomes and discover altered gene expression in saliva supernatant. Biomarkers discovered from the microarray study were subjected to clinical validation using an independent sample set of 30 pancreatic cancer patients, 30 chronic pancreatitis patients, and 30 healthy controls. Twelve messenger RNA biomarkers were discovered and validated. The logistic regression model with the combination of 4 messenger RNA biomarkers (KRAS, MBD3L2, ACRV1, and DPM1) could differentiate pancreatic cancer patients from noncancer subjects (chronic pancreatitis and healthy control), yielding a receiver operating characteristic plot, area under the curve value of 0.97 with 90 percent sensitivity and 95 percent specificity. The salivary biomarkers possess discriminatory power for the detection of resectable pancreatic cancer, with high specificity and sensitivity. The report also provides the proof of concept of salivary biomarkers for the noninvasive detection of a systemic cancer and paves the way for prediction model validation study followed by pivotal clinical validation [500].

Diabetes and pancreatic cancer

Glucose metabolism represents a complex system, and several components of the regulatory metabolic pathways may induce abnormalities in cellular growth and regulation. The strongest evidence of an association between glucose metabolism alterations and cancer derives from cohort studies, showing increased cancer incidence and mortality in the presence of diabetes. In particular, several studies clearly indicate an association between type 2 diabetes and the risk of colorectal, pancreatic, and breast cancer. An increased risk of

liver, gastric, and endometrial malignancies has also been suggested. Type 1 diabetes is associated with an elevated risk of female reproductive organs and gastric cancers. The risk of malignancies is also increased at earlier stages of glucose metabolism abnormalities, with a linear relationship between cancer risk and plasma insulin levels, usually elevated in the presence of metabolic syndrome or diabetes. The prevalence of diabetes and obesity is rapidly increasing worldwide; if these conditions are associated even with a small increase in the risk of cancer, this will translate into important consequences for public health [501].

Theoretical connections

Pancreatic cancer is strongly associated with the development of hyperglycemia, peripheral insulin resistance and diabetes mellitus, especially when presented as new-onset diabetes mellitus. Electronic searches were conducted to identify reports of published studies. Searches were restricted to articles published in English. The National Library of Medicine's PubMed database, including Medline citations from 1950 to 2009, was searched for articles on the development of cachexia in pancreatic cancer. Ninety-six articles met the criteria for combination of MeSH terms, out of which 73 articles were excluded due to irrelevant contents. A recent meta-analysis of 21 independent prospective studies supported a positive association between BMI and pancreatic cancer for both men and women. Insulin binds to the IGF1 (insulin-like growth factor 1) receptor and thereby increases the amount of available IGF1 (insulin-like growth factor binding protein 1), which in turn stimulates growth in exocrine PaC cells in an autocrine manner. Therefore, peripheral insulin resistance and hyperinsulinemia have been suggested to promote growth of pancreatic cancer cells, and therefore a relation between longstanding diabetes mellitus type 2 and pancreatic cancer has been implied. The anti-diabetic drug metformin reduces hyperglycemia and islet proliferation by suppressing hepatic gluconeogenesis and increasing glucose uptake in muscles. In a study, feeding one group of hamsters with metformin in drinking water from birth, while controls were left untreated, and then exposing all hamsters to a pancreatic carcinogen, resulted in 50 percent malignant lesions in untreated hamsters, whereas no malignancies were observed in the metformin-fed group. Epidemiological studies, though, give incongruent results to this problem. There are data supporting a tumor-derived influence on glucose metabolism, insulin secretion and eventually the development of diabetes mellitus in early stages of pancreatic cancer. During pregnancy many women develop a certain degree of peripheral insulin resistance due to weight gain and hormonal influence from the placenta. If the hyperglycemia is not compensated with increased insulin production, it sometimes leads to gestational diabetes mellitus (GDM). A population-based cohort study of 37,926 child-bearing Israeli women with a 28-40 years follow-up, showed a 7-fold increase in the relative risk for pancreatic cancer development for women with a history of GDM. A growing tumor is highly dependent on glycolysis for energy production, and by releasing substances that in a direct or non-direct way cause insulin resistance and hyperglycemia, the tumor guarantees its need of glucose. Peripheral insulin resistance associated with pancreatic cancer disturbs the insulin signaling cascade in skeletal muscle at many different steps, thereby causing multiple defects in glycogen synthesis and glucose storage. Both decreased glycogen synthase activity and increased glycogen phosphorylase activity have been shown in relation to pancreatic cancer, leading to the hyperglycemia commonly seen in cancer patients. Since no disturbances in skeletal muscle insulin receptor binding or receptor tyrosine-kinase activity have been reported, it is probable that the insulin resistance seen in pancreatic cancer patients is predominantly due to defects at the postreceptor level. Perhaps the strongest evidence for the tumor itself as a source for diabetogenic factor(s) are derived from the observation that glucose metabolism is improved after resection of some malignant pancreatic tumors, including removal of as much as 75 percent of the pancreas. Diabetes mellitus in pancreatic cancer is today clinically indistinguishable from diabetes type 2. Even glucose levels in the upper range of normal have been associated with an increased risk for development of pancreatic cancer. The only possibility for curative intent in pancreatic cancer is to diagnose the disease before symptoms occur. Patients with newly diagnosed diabetes

mellitus type 2 or hyperglycemia as a risk group have been recommended for primary screening for pancreatic cancer but to date, there is no specific biomarker to identify patients with an asymptomatic pancreatic cancer [502].

Genetic variations

Altered glucose metabolism is the most common metabolic hallmark of malignancies. The authors tested the hypothesis that glucose metabolism gene variations affect clinical outcome in pancreatic cancer. The authors retrospectively genotyped 26 single nucleotide polymorphisms from 5 glucose metabolism genes in 154 patients with localized disease and validated the findings in 552 patients with different stages of pancreatic adenocarcinoma. Association between genotypes and overall survival (OS) was evaluated using multivariate Cox proportional hazard regression models with adjustment for clinical predictors. Glucokinase (GCK) IVS1 + 9652C > T and hexokinase 2 (HK2) N692N homozygous variants were significantly associated with reduced OS in the training set of 154 patients. These associations were confirmed in the validation set of 552 patients and in the combined dataset of all 706 patients. In addition, HK2 R844K variant K allele was associated with a better survival in the validation set and the combined dataset. When data were further analyzed by disease stage, glutamine-fructose-6-phosphate transaminase (GFPT1) IVS14-3094T>C, HK2 N692N and R844K in patients with localized disease and GCK IVS1 + 9652C>T in patients with advanced disease were significant independent predictors for OS. Haplotype CGG of GPI and GCTATGG of HK2 were associated with better OS, respectively. Thus, the authors demonstrated that glucose metabolism gene polymorphisms affect clinical outcome in pancreatic cancer. These observations support a role of abnormal glucose metabolism in pancreatic carcinogenesis [503].

Metabolic syndrome

The aim of one study was to investigate the association between factors in metabolic syndrome (MetS; single and combined) and the risk of pancreatic cancer. The Metabolic Syndrome and Cancer Project is a pooled cohort containing data on body mass index, blood pressure, and blood levels of glucose, cholesterol, and triglycerides in 580000 individuals. During follow-up, 862 individuals were diagnosed with pancreatic cancer. Cox proportional hazards analysis was used to calculate relative risks (RR) with 95 percent confidence intervals using the above-mentioned factors categorized into quintiles and transformed into z-scores. The trend over quintiles was positively associated with the risk of pancreatic cancer for mid-blood pressure (mid-BP) and glucose in men and for body mass index, mid-BP, and glucose in women. The z-score for the adjusted mid-BP (RR 1.10; 95 % confidence interval 1.01 to 1.20) and the calibrated z-score for glucose (RR 1.37; 95 % confidence interval 1.14 to 1.34) were positively associated with pancreatic cancer in men. In women, a positive association was found for calibrated z-scores for mid-BP (RR 1.34; 95 % confidence interval 1.08 to 1.66), for the calibrated z-score for glucose (RR 1.98; 95 % confidence interval 1.41 to 2.76), and for the composite z-score for MetS (RR 1.58; 95 % confidence interval 1.34 to 1.87). Thus, the study adds further evidence to a possible link between abnormal glucose metabolism and risk of pancreatic cancer [504].

Effects of insulin

Diabetes mellitus is a chronic disease that affects > 23.6 million Americans, and occurs when the body is unable to produce or becomes resistant to endogenous insulin. This alteration of insulin's action reduces adequate utilization of glucose transporter type 4 (GLUT4) receptors, which are responsible for cellular glucose uptake. Thus, exogenous administration of human insulin and insulin analogs is an important modality used to reduce morbidity and mortality in both type 1 and type 2 diabetes. According to 2007 estimates, 27 percent of all patients with

diabetes use some form of insulin therapy. The increasing utilization of insulin has become a cause for concern because findings from several observational trials have suggested an association with an increased risk of developing cancer. To help elucidate the potential interplay between insulin use and cancer, it was searched PubMed and MEDLINE to identify articles that assessed the carcinogenic and/or mitogenic potential of diabetes treatments, focusing on insulin specifically. Data from our review suggest that insulin analogs, particularly insulin glargine, may play more of a mitogenic than a carcinogenic role in association with different types of cancer, suggesting an amplified rate of existing tumor growth in the presence of insulin analogs. Evidence for insulin-induced mitogenicity appears to be most prevalent in prostate, breast, pancreatic, and colorectal cancers. In conclusion, the positive effects of insulin therapy on reducing morbidity and mortality in diabetes greatly outweigh the risks at this time. However, clinicians must be diligent in both screening for new cancers in patients receiving insulin and in monitoring for tumor growth or maintenance of remission in patients with existing cancers [505].

Negative effects on the progression of adenocarcinomas by hyperinsulinaemia and the insulin analogue glargine (A21Gly,B31Arg,B32Arg human insulin) have recently been suggested. Most actions of this insulin analogue have hitherto been explained by direct stimulation of growth potential of neoplastic cells and by its IGF-1 related properties. However, insulin-stimulated angiogenesis could be an additional factor involved in tumour progression and clinical outcomes associated with cancer. Five types of human adenocarcinoma (breast, colon, pancreas, lung and kidney) were evaluated for the presence of insulin receptors (IRs) on angiogenic structures. In an in vitro angiogenesis assay, various commercially available insulin compounds were evaluated for their potential to increase capillary-like tube formation of human microvascular endothelial cells (hMVEC). Insulin compounds used were: human insulin, insulin lispro (B28Lys,B29Pro human insulin), insulin glargine and insulin detemir (B29Lys[e-tetradecanoyl],desB30 human insulin). Insulin receptors were found to be strongly expressed on the endothelium of microvessels in all evaluated adenocarcinomas, in addition to variable expression on tumour cells. Low or no detectable expression of IRs was seen on microvessels in extratumoral stroma. Incubation with commercially available insulin compounds increased capillary-like tube formation of hMVEC in vitro. The results suggest that all tested insulin compounds may stimulate tumour growth by enhancing local angiogenesis [506].

Westernized lifestyle

Over the last 60 years, Japanese people have experienced a rapid and drastic change in lifestyle, including diet. Suspicions have been raised that so-called westernization, characterized by a high-calorie diet and physical inactivity, is associated with increasing trends in the incidence of cancer of the colon, liver, pancreas, prostate, and breast, as well as type 2 diabetes. Epidemiological evidence from our prospective study, the Japan Public Health Center-based Prospective (JPHC) study, and systematic literature reviews generally support the idea that factors related to diabetes or insulin resistance are associated with an increased risk of colon (mostly in men), liver, and pancreatic cancers. These cancers are inversely associated with physical activity and coffee consumption, which are known to decrease the risk of type 2 diabetes. The suggested mechanism of these effects is that insulin resistance and the resulting chronic hyperinsulinemia and increase in bioavailable insulin-like growth factor 1 (IGF1) stimulate tumor growth. In contrast, associations with diabetes are less clear for cancer of the colon in women, and breast and prostate, which are known to be related to sex hormones. The effect of insulin resistance or body fat on sex-hormone production and bioavailability may modify their carcinogenic effect differently from cancers of the colon in men, and liver and pancreas. In conclusion, there is substantial evidence to show that cancers of the colon, liver, and pancreas are associated with insulin resistance, and that these cancers can be prevented by increasing physical activity, and possibly coffee consumption [507].

Symptoms and signs

Pancreaticopleural fistula

A 63-year-old man was admitted with left pleural effusion, and a very high amylase level. A diagnosis of pancreaticopleural fistula was made, based on the findings of magnetic resonance cholangiopancreatography and endoscopic retrograde pancreatography (ERP). After the placement of an endoscopic naso-pancreatic drainage tube, the pleural effusion markedly reduced. When ERP was performed for internal drainage, the main pancreatic duct and stricture were biopsied and showed pancreatic ductal adenocarcinoma histologically. CT revealed a mass in the head of the pancreas. He underwent pylorus-preserving pancreaticoduodenectomy [508].

Pain

Pancreatic neuropathy in chronic pancreatitis (CP) and pancreatic cancer (PCa) is characterized by pancreatic neuropathy, i.e. increased neural density and hypertrophy, which are associated with neuropathic pain. Dissociated myenteric plexus (MP) and dorsal root ganglia (DRG) neurons of newborn rats were treated with normal human pancreas (NP), CP or PCa tissue extracts. Furthermore, MP and DRG neurons were cultured in supernatants from different pancreatic cancer cell lines (PCC) and human pancreatic stellate cells (hPSC) obtained from either CP or PCa tissues. For analysis, the neurite density, outgrowth, neuronal branching capacity and perikaryonal size were quantified. Myenteric plexus and DRG neurons grown in CP and PCa tissue extracts built denser networks than in NP extracts. Both neuronal types showed a strong neurite outgrowth, more complex branching pattern and a somatic hypertrophy in CP and PCa extracts. Pancreatic cancer cell supernatants induced a prominent neurite outgrowth, increased neurite density and perikaryonal hypertrophy in MP and DRG neurons. Supernatants of CP-derived hPSC strongly stimulated neurite outgrowth. Glial density in MP cultures was strikingly increased by PCa tissue extracts. It was concluded that intrapancreatic microenvironment in CP and PCa induces neuroplastic alterations under in-vitro conditions, leading to increased neural density and hypertrophy. Thus, due to its neurotrophic attributes, the intrapancreatic microenvironment in CP and PCa seems to be a key player in the generation of pancreatic neuropathy and neuroplasticity [509].

Diagnosics

Ultrasonography

It was reported the sonographic, CT, and MRI findings in a case of focal fatty infiltration of the pancreas. Sonography revealed an echogenic mass in pancreas head. On CT, the mass was hypodense. The mass showed same signal intensity to the surrounding normal pancreas on in-phase T1-weighted MR images and a loss of signal intensity on opposed-phase MR images [510].

EUS

Early diagnosis and appropriate staging of pancreatic adenocarcinoma is of vital importance to possibly detect this otherwise lethal disease at a curable phase and to stratify patients who would benefit the most from surgical resection. The availability of endoscopic ultrasound (EUS) with its unique capability of obtaining refine images of the pancreas has represented a major breakthrough in the management of these difficult tasks. Furthermore, the ability to perform fine needle aspiration (FNA) under real time EUS guidance has offered the

possibility to reach a definite diagnosis which has a major impact on the decision making process in the care of patients with both resectable and unresectable pancreatic cancer. In parallel to the widespread importance of diagnostic EUS, the therapeutic applications of EUS are increasing and may further expand the role of this procedure in the management of pancreatic cancer. One article focused on the current role of EUS and EUS-FNA in the diagnosis and staging of solid pancreatic lesions in different clinical scenarios, including those individuals at a high risk of developing pancreatic cancer and who may be candidates for a EUS-based screening and surveillance program [511].

The value of repeating endoscopic ultrasound (EUS) is seldom described. One study evaluated a patient population in which EUS was repeated. It was a retrospective study of patients who between 2002 and 2006 had an EUS scan performed; this EUS scan (re-EUS) was the second or more EUS scan performed. Over the study period, the department performed 3024 EUS procedures, of which 561 investigations were defined as re-EUS. According to defined exclusion criteria, 244 procedures were not analyzed further. The study group thus consisted of 317 procedures (242 patients). In 163 cases (126 patients), re-EUS was planned by the endosonographer for control of an undetermined lesion. The first re-EUS scan performed changed the further management in 91 of 126 patients (72 %). Sensitivity and specificity of re-EUS regarding pancreatic cancer were 0.65 and 1.00, respectively. Re-EUS was performed in 82 cases (77 patients) where no re-investigation had been planned at the initial EUS scan but worsening of symptoms or new findings of other imaging procedures had led to an additional EUS scan. Thirteen of these patients (17 %) proved to have pancreatic cancer. In 62 cases (57 patients) re-EUS and EUS-guided fine-needle aspiration (FNA) had been planned in order to confirm the suspicion of malignant disease. Following re-EUS and EUS-FNA, 40 of these patients could be referred for either oncology or surgery. In the remaining 10 cases, re-EUS was performed for miscellaneous indications. The authors concluded that re-EUS has a substantial clinical impact on the further management of the patient [512].

CT

Chronic pancreatitis and pancreatic adenocarcinoma often show similar clinical and imaging appearances. One study aimed to differentiate chronic pancreatitis from pancreatic adenocarcinoma by defining enhancement patterns in both pathologic conditions during triple-phase helical CT. The study included 42 patients with chronic pancreatitis and 85 patients with pancreatic adenocarcinoma. CT images obtained according to protocol A (scan delays, 30, 60, and 150 s; 300 mg I/mL contrast material) or protocol B (scan delays, 40, 70, and 150 s; 370 mg I/mL contrast material) were retrospectively evaluated. Mean contrast enhancement value of normal pancreas peaked in the first phase (early-washout pattern) while that of chronic pancreatitis peaked in the second phase (delayed-washout pattern), and that of pancreatic adenocarcinoma gradually rose (increasing pattern) in both protocols. Diagnostic indices for pancreatic adenocarcinoma were 82 percent and 94 percent for sensitivity, 83 percent and 83 percent for specificity, 83 percent and 90 percent for accuracy in protocols A and B, respectively, when differentiation between chronic pancreatitis and pancreatic adenocarcinoma was performed based on time-attenuation curve patterns. The results indicate that time attenuation curves obtained from triple-phase helical CT in protocol B provide useful information in differentiating chronic pancreatitis from pancreatic adenocarcinoma [513].

Preoperative assessment of pancreatic masses is still challenging as regards the characterization and assessment of irresectability. The opportunities of modern multidetector computed tomography (MDCT) with image postprocessing can be expected to enhance the diagnostic performance if accurate criteria are elaborated. To estimate the accuracy of MDCT and multiplanar image reconstructions with the use of standardized imaging criteria for preoperative evaluation of pancreatic masses with respect to irresectability a total of 105

consecutive patients who underwent exploratory laparoscopy or pancreatic resection and had preoperative 3-phase MDCT (4-64 rows) were enrolled retrospectively. First, transverse sections and secondly additional 3Ds were reviewed by two independent blinded observers (O1/O2). Preoperative imaging findings were correlated with intraoperative and histopathologic results. Among all 105 patients, 70 malignant pancreatic tumors and 35 benign pancreatic diseases were found (accuracy of 93 % for O1 and 91 % for O2). For arterial tumor invasion, receiver operator characteristic (ROC) analysis (values averaged from the results of O1 and O2) revealed an area under the curve (AUC) of 0.93 for transverse sections and 0.99 for 3Ds. Regarding irresectability, positive predictive values were 97 percent (with 3Ds, 97 %) for O1/O2; negative predictive values were 84 percent (with 3Ds, 89 %) for O1 and 86 percent (with 3Ds, 91 %) for O2. It was concluded that MDCT with 3Ds was highly accurate for evaluation and assessment of irresectability criteria in patients with pancreatic masses. However, due to the limited specificity regarding arterial tumor infiltration, the indication for surgical exploration should be made generously in case of inconclusive findings [514].

To retrospectively determine the frequency, clinical and pathologic characteristics, and computed tomographic (CT) findings of visually isoattenuating pancreatic adenocarcinomas and to investigate the utility of magnetic resonance (MR) imaging and positron emission tomography (PET)/CT for detecting them, 743 consecutive patients with pathologically proved pancreatic cancer, 644 patients (392 men, 252 women; mean age, 60 years \pm 10) who had undergone both arterial and portal phase contrast material-enhanced CT were included. Visually isoattenuating pancreatic adenocarcinoma was defined as lesion isoattenuation in both scan phases. Serum levels of carbohydrate antigen 19-9, immunoglobulin G (IgG), and IgG fraction 4 (IgG4), survival after curative-intent surgery; and pathologic findings of visually isoattenuating pancreatic adenocarcinomas were analyzed. CT findings of visually isoattenuating pancreatic adenocarcinomas and the sensitivity of MR imaging and PET/CT for detecting them were determined. The frequency of visually isoattenuating pancreatic adenocarcinomas among pancreatic cancers was 5 percent (35 of 644). Serum levels of carbohydrate antigen 19-9, IgG, and IgG4 were elevated in 52 percent (17 of 33), 8 percent (one of 12), and 8 percent (one of 12) of patients, respectively. Visually isoattenuating pancreatic adenocarcinoma, compared with usual pancreatic adenocarcinoma, was independently associated with a better survival after curative-intent surgery: Adjusted hazard ratio was 0.430. Thirty surgically resected visually isoattenuating pancreatic adenocarcinomas were 1.5-4 cm (median, 3 cm). Their pathologic findings differed from those of usual pancreatic adenocarcinomas: lower tumor cellularity, more frequent intratumoral acinar tissue and islet cells, and less prominent tumor necrosis. Visually isoattenuating pancreatic adenocarcinomas showed various abnormalities at CT, which may suggest an isoattenuating mass or nodule. Sensitivities of MR imaging and PET/CT were 79 percent (19 of 24) and 74 percent (14 of 19), respectively. It was concluded that visually isoattenuating pancreatic adenocarcinoma represents a small but meaningful subset of pancreatic cancer and has characteristic clinical and pathologic features. MR imaging and PET/CT may be useful as subsequent examinations when the patient is suspected of having the lesion at CT [515].

The aim of the study was to retrospectively compare image findings of poorly enhanced areas (PEAs) of pancreatic adenocarcinomas that show almost no enhancement or obviously hypoattenuating area relative to the surrounding carcinoma on late-phase dynamic computed tomography (CT) with pathological findings. Thirty-nine patients with pancreatic adenocarcinoma underwent dynamic CT and surgery. Poorly enhanced areas were classified according to their size, attenuation value, position, and border on CT imaging and signal intensity on magnetic resonance imaging. Of the 33 PEAs, 12 showed neoplastic duct-like structure that contained both large tumor gland and dilated pancreatic duct with atypia, 11 showed necrosis, 4 showed retention cyst, 2 showed dilated pancreatic duct without atypia or with limited invasion, 1 showed mucin, and 3 showed no remarkable differences in

characteristics compared with surrounding tissue. Neoplastic duct-like structures tended to be well defined. Necrotic portions tended to show a high attenuation value and central position and were ill defined. Retention cysts tended to show a peripheral position. It was concluded that poorly enhanced areas corresponded to cystic, necrotic, and mucinous components. Image findings demonstrated these characteristics. Necrotic component can be visualized and distinguished with other components and can be a prognostic factor [516].

Lymphatic invasion

Peripancreatic lymphatic networks are frequently involved in pancreatobiliary carcinoma, affecting the prognosis. However, little attention has been paid to CT imaging of normal and pathological conditions of peripancreatic lymphatic networks. It was therefore evaluated multi-detector row CT (MDCT) images of peripancreatic lymphatic networks invaded by pancreatic carcinoma and compared them with those of normal peripancreatic lymphatic networks using imaging reconstruction every 1 mm with a multiplanar reformation technique. Apart from the region around the pancreatic body and tail, normal peripancreatic lymphatic networks were detected as "linear structures" on MDCT. However, peripancreatic lymphatic invasion by pancreatic carcinoma was frequently identified as "reticular," "tubular," or "soft tissue mass" appearances in the peripancreatic fat tissues. Peripancreatic lymphatic invasion by pancreatic carcinoma was more frequently detected around the common hepatic artery, celiac artery, superior mesenteric artery, and left para-aortic area. Depending on the tumor location, positive peripancreatic lymphatic invasion was most frequent at the area around the common hepatic artery in the head region and at the area around the celiac artery in the body and tail regions. Knowledge of CT imaging of normal and pathological peripancreatic lymphatic networks is essential for determining the accurate staging of pancreatic carcinoma [517].

Fibrosis

To demonstrate the contrast-enhancement behavior of pancreatic carcinoma on dynamic contrast-enhanced CT (DCE-CT), and the relationship between the degree of contrast-enhancement and the vascularity (vessel density) and amount of fibrous stroma (fibrosis within the tumor) on pathological specimen the contrast-enhancement values were measured by producing the subtracting images for obtaining largest region of interests to reduce measurement errors and variability. Vascularity was determined by immunostaining of the tissue sections with factor 8 and the fibrous stroma was determined by picosirius staining. Correlation of the findings of DCE-CT with pathological findings was performed in 21 patients with pancreatic carcinoma. All but one patient exhibited a gradually increasing enhancement, but there was considerably wide range in contrast-enhancement values of tumors. Examination of the overall relationship between vascularity and fibrous stroma with contrast-enhancement behavior showed that tumor with more fibrosis and higher vascularity had a higher contrast effect through all phases of dynamic study. Tumors having liver metastases tended to be less fibrotic than tumors without liver metastases. It was concluded that the contrast-enhancement behavior of pancreatic carcinoma may be helpful in estimating vascularity and the extent of tumor fibrosis and possibility of liver metastases [518].

Low-tube-voltage, high-tube-current

To investigate whether an adaptive statistical iterative reconstruction (ASIR) algorithm improves the image quality at low-tube-voltage (80-kVp), high-tube-current (675-mA) multidetector abdominal computed tomography (CT) during the late hepatic arterial phase a prospective, single-center HIPAA-compliant study was performed. Ten patients (six men, four women; mean age, 63 years; age range, 51-77 years) known or suspected to have hypervascular liver tumors underwent dual-energy 64-section multidetector CT. High- and low-tube-voltage CT images were acquired sequentially during the late hepatic arterial phase of contrast enhancement. Standard convolution FBP was used to reconstruct 140-kVp (protocol A) and 80-kVp (protocol B) image sets, and ASIR (protocol C) was used to reconstruct 80-kVp image sets. The mean image noise; contrast-to-noise ratio (CNR) relative

to muscle for the aorta, liver, and pancreas; and effective dose with each protocol were assessed. A figure of merit (FOM) was computed to normalize the image noise and CNR for each protocol to effective dose. Repeated-measures analysis of variance with Bonferroni adjustment for multiple comparisons was used to compare differences in mean CNR, image noise, and corresponding FOM among the three protocols. The noise power spectra generated from a custom phantom with each protocol were also compared. When image noise was normalized to effective dose, protocol C, as compared with protocols A and B, yielded an approximately twofold reduction in noise. When the CNR was normalized to effective dose, protocol C yielded significantly higher CNRs for the aorta, liver, and pancreas than did protocol A and a significantly higher CNR for the liver than did protocol B. Mean effective doses were $17.5 \text{ mSv} \pm 0.6$ (standard error) with protocol A and $5.1 \text{ mSv} \pm 0.3$ with protocols B and C. Compared with protocols A and B, protocol C yielded a small but quantifiable noise reduction across the entire spectrum of spatial frequencies. Compared with standard FBP reconstruction, an ASIR algorithm improves image quality and has the potential to decrease radiation dose at low-tube-voltage, high-tube-current multidetector abdominal CT during the late hepatic arterial phase [519].

The purpose of one study was to determine whether the conspicuity of malignant tumors of the pancreas at dual-source dual-energy CT is better with 80-kVp acquisition than with 120-kVp acquisition simulated with a weighted average. Fifteen patients with pancreatic adenocarcinoma underwent contrast-enhanced dual-source dual-energy CT. The abdominal diameter of all patients was 35 cm or less. Data were reconstructed as a weighted average of the 140- and 80-kVp acquisitions, simulating 120 kVp, and as a pure 80-kVp data set. A region-of-interest cursor was placed within the tumor and the adjacent normal parenchyma, and attenuation differences and contrast-to-noise ratios were calculated for pancreatic tumors at 80 kVp and with the weighted-average acquisition. The 80-kVp and weighted-average images were subjectively compared in terms of lesion conspicuity, image quality, and duct visualization. The mean difference in attenuation for each pancreatic tumor and adjacent portion of normal pancreas was 83.3 ± 29.6 (SD) HU at 80 kVp and 49.4 ± 23.0 HU at weighted-average 120 kVp. Adenocarcinoma attenuation differences were significantly greater at 80 kVp than at 120 kVp. Contrast-to-noise ratio was significantly higher at 80 kVp than at 120 kVp. Subjective analysis showed lesion conspicuity and duct visualization were significantly better on the 80-kVp images. It was concluded that at portal venous phase dual-source dual-energy CT, the conspicuity of malignant tumors of the pancreas is greater at 80 kVp than with weighted-average acquisition [520].

CT versus MRI

One study compared the results of multislice computed tomography (MSCT) and high-field magnetic resonance imaging (MRI) in the diagnostic evaluation of pancreatic masses. Forty patients with clinical and ultrasonographic evidence of pancreatic masses underwent MSCT and MRI. The majority of patients (31/40, 78 %) had proven malignant pancreatic tumours (24 ductal adenocarcinoma, six mucinous cystadenocarcinoma, one intraductal papillary mucinous carcinoma), whereas the remaining patients (9/40, 22 %) were found to have benign lesions (eight chronic pancreatitis, one serous cystadenoma). Results of the imaging studies were compared with biopsy (n=33) and/or histology (n=7) findings to calculate sensitivity, specificity, accuracy and positive (PPV) and negative (NPV) predictive value for correct identification of tumours and evaluation of resectability of malignancies. Both for tumour identification and resectability, MSCT and MRI had comparable diagnostic accuracy, with no statistically significant differences between them.

	<i>CT</i>	<i>MRI</i>
Tumor identification (%)		
accuracy	98	98
sensitivity	100	100
specificity	88	88
PPV	97	97
NPV	100	100
Tumor respectability (%)		
accuracy	94	90
sensitivity	92	88
specificity	100	100
PPV	100	100
NPV	78	70

It was concluded that MRI represents a valid diagnostic alternative to CT in the evaluation of patients with pancreatic masses, both for correct identification and characterisation of primary lesions and to establish resectability in the case of malignancies. New high-field MRI equipment allows optimal imaging quality with good contrast resolution in evaluating the upper abdomen [521].

MRI

The time-signal intensity curve (TIC) of the pancreas obtained from dynamic contrast-enhanced magnetic resonance imaging closely reflects the histological degree of pancreatic fibrosis. Seventy-six patients who had undergone a pancreatic TIC analysis prior to receiving a pancreaticoduodenectomy for various reasons were subjected to a yearly monitoring with pancreatic TIC for the pancreatic remnants. The pancreatic TIC profiles were classified into 3 types: type I, indicating a normal pancreas without fibrosis; and types II and III indicating fibrotic pancreas. The preoperative pancreatic TICs were type-I in 51 patients, type-II in 20, and type-III in 5, and the corresponding pancreatic fibrosis ratios were proved histologically to be 4 percent, 13 percent, and 21 percent, respectively. The mean postoperative follow-up period was 40 months. A type-I changed to type-II in 16 patients by 32 months after surgery. In these patients, the exocrine remnant pancreatic function was preserved at the time of TIC conversion, but it significantly deteriorated thereafter. Pancreatic anastomotic leakage was found to be a significant risk factor predisposing a patient to undergo postoperative TIC conversion. In contrast, a preoperative type-II or III showed a postoperative conversion to type-I or II in 6 patients. In this group, the exocrine pancreatic function was noted to show a good recovery. In 35 patients who had a type-I TIC throughout the study, the remnant pancreatic function was well maintained. It was concluded that pancreatic TIC analysis has the ability to detect an early fibrotic change that precedes a functional deterioration of the pancreatic remnant after a pancreaticoduodenectomy. Following a pancreatoduodenectomy, some patients show an improvement in pancreatic fibrosis, but they may also experience remnant pancreatic fibrosis when pancreatic anastomotic leakage occurs after surgery [522].

Correlation to histopathology

To determine whether the degree of enhancement of pancreatic adenocarcinoma visualized on arterial phase gadolinium-enhanced magnetic resonance imaging (MRI) correlates with the histopathological tumor grade 39 patients with pancreatic adenocarcinoma had MRI within 14 days before tumor resection. Gadolinium-chelate-enhanced (Gd) 3-dimensional gradient echo images were acquired including the arterial phase. Tumor imaging patterns on the arterial phase images were classified for low, moderate, or high degree of enhancement and compared against conventional histological grading. Based on histological grading, there were 12 poorly differentiated, 2 poorly to moderately differentiated, 22 moderately differentiated, and 3 well-differentiated adenocarcinomas. There was agreement between the

MRI arterial enhancement pattern and histological grading in 30 of 39 cases. The mean size of tumors grouped by enhancement pattern or grade was not significantly different between groups. Although minor discordance was found in 9 of the 39 cases, statistical analysis showed agreement between the degree of arterial enhancement on MRI and histological tumor differentiation [523].

FDG-PET

Although surgical resection is the only curative therapeutic option for recurrent or metachronous pancreatic carcinomas, most such cancers are beyond surgical curability. We herein report on two rare cases of remnant pancreatectomy used to treat recurrent or metachronous pancreatic carcinomas. A 65-year-old male developed weight loss and diabetes mellitus 83 months after a pylorus-preserving pancreaticoduodenectomy followed by two years of adjuvant chemotherapy (5-fluorouracil plus leucovorin plus mitomycin C) for a pancreatic carcinoma in the head of the pancreas (stage IA). An abdominal CT scan revealed a 3 cm tumor in the remnant pancreas which appeared as a “hot” nodule on FDG-PET. A remnant distal pancreatectomy was performed and a pancreatic carcinoma similar in profile to the primary lesion (stage IIB) was confirmed pathologically. In another case a 67-year-old male showed increased CA 19-9 levels 25 months after a distal pancreatectomy for a pancreatic carcinoma in the body of the pancreas (stage IA). An abdominal CT scan revealed a cystic lesion in the cut end of the pancreas which appeared as a “hot” nodule on FDG-PET. A remnant proximal pancreatectomy with duodenectomy was performed and a metachronous pancreatic carcinoma (stage III) was confirmed pathologically. It was concluded that FDG-PET can play a key role in detecting remnant pancreatic carcinomas [524].

FNA

FNA is an important aspect in the diagnosis and management of pancreatic masses. Studies have shown that the overall accuracy of EUS-guided FNA ranges between 71 percent and 90 percent in this setting. It is important to review all pertinent clinical data (especially cross-sectional imaging) before performing endoscopy. The choice of needle may depend on the location and size of the lesion. Once the lesion is targeted and placed in optimal position, FNA is performed under total EUS guidance while visualizing the needle tip at all times. Factors that may increase the diagnostic yield of FNA include sampling the lesion in multiple planes, targeting the margins or firmer ends of a necrotic mass, and arranging for ROSE [525].

Pancreatic cancer can be difficult to diagnose. Fine-needle aspiration (FNA) biopsies may be negative even when malignancy is present. To identify endosonographic features predictive of malignancy that will separate patients into high- and low-risk groups, in whom a negative FNA effectively rules out malignancy patients presenting for endoscopic ultrasound (EUS) evaluation for suspected pancreatic mass were prospectively enrolled. If a mass or abnormal lymph nodes were present, sampling via fine-needle aspiration (FNA) was performed. The characteristics of patients with cancer were compared to the characteristics of patients without cancer using Chi-square testing and t-tests. Seventy-three patients were enrolled. Thirty-three patients had cancer and 40 had benign disease. On multivariate analysis, only vascular or organ invasion and dilation of the pancreatic duct (PD) were significantly associated with cancer. PD dilation was examined as a stand-alone feature. The presence of a dilated PD placed patients into a group with a 65 percent prevalence of malignancy. In the non-dilated PD group, the prevalence of malignancy was only 17 percent, and in this group, the negative predictive value of FNA was 100 percent, compared to an NPV of 73 percent in the entire cohort. It was concluded that the most significant negative predictive endosonographic finding in patients with suspected pancreatic cancer is a non-dilated PD. If

a patient with suspected pancreatic cancer does not have a dilated pancreatic duct and the FNA is negative for malignancy, the likelihood of cancer is low [526].

To investigate the value of EUS-guided FNA in the diagnosis of solid and cystic pancreatic tumor(-like) lesions as well as metastatic tumor growth within peripancreatic lymph nodes and its impact on therapeutic decision-making the results of the cytologic and pathohistological investigation were compared with each other and the detection rates of various imaging procedures. Overall, 153 patients (mean age, 57 years) underwent EUS-guided FNA from 2000 to 2003. Comparing various imaging procedures such as CT scan (80 %), MRI (57 %) and abdominal US (89 %), EUS achieved the highest diagnostic accuracy: 100 percent. For EUS-based T-staging in 26 patients with malignant tumor lesions undergoing surgical intervention, there was a sensitivity of 73 percent (specificity, 86 %; PPV, 69 %; NPV, 84 %), while the parameters for N-staging (n=25) were: sensitivity, 62 percent; specificity, 75 percent; NPV, 64 percent; PPV, 72 percent. While the sensitivity of EUS-guided FNA in the group of patients who underwent surgical intervention (n=55) was 81 percent (specificity, 75 %; PPV, 92 %; NPV, 53 %), the parameters were as follows in the subgroup of individuals with chronic pancreatitis (n=30): sensitivity in detecting a malignant pancreatic tumor lesion, 50 percent; specificity, 92 percent; PPV, 60 percent; and NPV, 88 percent. Based on preoperative characteristics such as suspected diagnosis, TNM stage and tumor entity, a surgical intervention could be avoided in 29/153 patients (19 %). It was concluded that EUS-guided FNA allows more precise diagnosis clarification (malignant tumor growth and tumor entity) in solid and cystic pancreatic tumor(-like) lesions, which may assist in early and sufficient therapeutic decision-making [527].

Endoscopic ultrasound (EUS) fine needle aspiration (FNA) can result in false-positive cytology and can also cause needle tract seeding. The goal was to evaluate a potential cause, namely, the presence of malignant cells within gastrointestinal luminal fluid, either as a result of tumor sloughing from luminal cancers or secondary to FNA of extraluminal sites. During EUS, luminal fluid that is usually aspirated through the echoendoscope suction channel and discarded was instead submitted for cytological analysis among patients with cancer and benign disease. Pre- and post-FNA luminal fluid samples were collected to discern the role of FNA in inducing a positive cytology. When not performing FNA, one sample was collected for the entire examination. The final diagnosis was based on strict clinicopathological criteria and ≥ 2 -year follow-up. The study was conducted in a tertiary referral center. It was assessed the prevalence of luminal fluid-positive cytology among patients with luminal (e.g. esophageal), extraluminal (e.g. pancreatic), and benign disease. Among the 140 patients prospectively enrolled with sufficient sampling and follow-up, an examination of luminal fluid cytology showed positive results for malignancy in luminal and extraluminal cancer patients, 48 and 10 percent, respectively. This included 8 out of 23 esophageal, 4 of 5 gastric, and 9 of 15 rectal cancers. The positive luminal fluid cytology rate with luminal cancers was not affected by performing FNA. Post-FNA luminal fluid cytology was positive in 3 out of 26 with pancreatic cancers. Cytological examination of luminal fluid aspirates did not demonstrate malignant cells in any patient with nonmalignant disease. It was concluded that malignant cells are commonly present in the GI luminal fluid of patients with luminal cancers and can also be found in patients with pancreatic cancer after EUS FNA [528].

It was assessed the incidence and outcome of pancreaticoduodenectomy for patients with a pre-operative benign diagnosis and in patients who had an unexpected diagnosis of benign disease following resection. It was also compared how the introduction of endoscopic ultrasound fine needle aspiration (EUS-FNA) has altered our pre-operative assessment. Between 1997 and 2006, 499 patients underwent pancreaticoduodenectomy. Data were collected prospectively. A further 85 patients between 2006 and 2008 had a different diagnostic approach (after imaging these patients have been also studied by EUS-FNA). Overall, 78 (16 %) patients had no malignant disease on final histology. Out of 459 patients

who underwent pancreaticoduodenectomy for presumed malignancy, 49 (11 %) had benign disease (sensitivity, 97 %; positive predictive value, 89 %). In a further 40 patients with a pre-operative benign diagnosis, it was found 11 cases (27 %) of malignancy (sensitivity, 37 %; negative predictive value, 72 %). Following the introduction of EUS-FNA, the sensitivity and specificity of the diagnostic work were 92 percent and 75 percent, respectively (positive predictive value, 93 percent; negative predictive value, 63 percent). The median follow-up was 35 months (range, 1-116 months). Prior to the introduction of EUS-FNA, a significant number of patients, in whom pancreaticoduodenectomy is carried out for suspected benign disease, turn out to have an underlying malignancy. The use of EUS-FNA has improved the specificity of diagnostic work-up [529].

The objective of one study was to report the incidence of bleeding after imaging-guided percutaneous core biopsy at a single center using a standardized technique in a retrospective review of percutaneous core biopsies performed at one institution from 2002 through 2008. Data were collected at the time of biopsy, and clinical information was obtained 24 hours and 3 months after the biopsy. The specific information that was collected included the results of coagulation studies, aspirin use, the organ biopsied, the size of the biopsy needle, and the number of needle passes. Bleeding complications were defined using the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) established by the National Cancer Institute. Among the 15,181 percutaneous core biopsies performed during the study period, 70 hemorrhages (0.5 %) that were CTCAE grade 3 or greater were identified within 3 months of biopsy. The incidence of bleeding in patients taking aspirin within 10 days before biopsy was 0.6 percent (18/3195), which was not statistically different compared with the incidence of bleeding in those not taking aspirin (52/11,986, 0.4 %). The incidence of bleeding after liver biopsy was 0.5 percent; kidney biopsy, 0.7 percent; lung biopsy, 0.2 percent; pancreas biopsy, 1.0 percent; and other biopsy, 0.2 percent. There were significant associations between major bleeding and serum platelet count and international normalized ratio, although the association between major bleeding and the size of the biopsy needle was not significant. It was concluded that the overall incidence of major bleeding after imaging-guided percutaneous core needle biopsy is low. Recent aspirin therapy does not appear to significantly increase the risk of such bleeding complications [530].

Immunohistochemistry

To evaluate whether B72.3 and CEA could identify duodenal and gastric contamination in cell blocks of clinically proven cases of pancreatic ductal carcinoma, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) cell blocks of pancreatic fine needle aspirates from 19 ductal adenocarcinomas, 9 IPMNs, 5 MCNs, and 22 cases containing gastrointestinal epithelial contamination (GIC) (7 gastric, 15 duodenal) were stained with antibody to carcinoembryonic antigen (CEA) and B72.3. CEA was positive in 89 percent of adenocarcinomas and 92 percent of mucinous lesions. It was never expressed in gastric contamination and was positive in 2/15 (13 %) duodenal contaminants. B72.3 was positive in 95 percent of adenocarcinomas and 85 percent of mucinous lesions. It was positive in 2/7 (28 %) gastric and 7/15 (47 %) duodenal contaminants. In contrast to previous work, these preliminary results indicate that B72.3 expression cannot be reliably used to identify GIC. A lack of CEA expression, however, can be used to identify both gastric and duodenal contamination. This represents an important diagnostic aid in the evaluation of suspected low grade mucinous lesions [531].

Telecytology

On-site evaluation of fine-needle aspiration (FNA) specimens by a pathologist is essential to obtain adequate samples and provide a preliminary diagnosis. Distance from the laboratory can make this difficult. The authors presented their experience with on-site evaluation using telecytology. Dynamic images of cytology smears were captured and processed with a Nikon digital camera system for microscopy and transmitted via Ethernet. A pathologist accessed the real-time images on a computer and interpreted them while communicating

with on-site operators over the telephone. Sample adequacy and accuracy of preliminary diagnosis were compared with those obtained by regular on-site evaluation. A total of 429 telecytopathology cases and 363 conventional on-site cases were compared. Specimens were mainly from the pancreas, gastrointestinal tract, liver, and lymph nodes. Adequacy rate was 94 percent for telecytopathology and 98 percent for conventional cases. Preliminary diagnoses (%) was

	<i>unsatisfactory</i>	<i>negative/benign</i>	<i>atypical</i>	<i>neoplasm</i>	<i>suspicious</i>	<i>positive for malignancy</i>
Telemedicine	6	15	18	7	8	32
Conventional	4	22	10	5	5	24

Preliminary and final diagnoses were discrepant in 7 (2 %) of 371 telecytopathology cases, and in 8 (3 %) of 252 conventional cases. Difficulty was encountered in some cases in distinguishing pancreatic endocrine neoplasm from lymphoid proliferations, and low grade pancreatic tumors from chronic pancreatitis via telecytopathology. It was concluded that on-site evaluation of FNA specimens via telecytopathology assures sample adequacy and accurate preliminary diagnosis compared with the conventional method. It allows pathologists to use their time more efficiently and makes on-site evaluations at remote locations possible [532].

Anaplastic carcinoma

Anaplastic carcinoma of the pancreas (ACP) is an aggressive variant of ductal adenocarcinoma. The aim of one study was to describe a single-center experience with the use of endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA) for the diagnosis of ACP. The cytology and surgical pathology databases were searched for a diagnosis of ACP between 1992 and 2008. Demographic, clinical, surgical, radiographic, pathological, and EUS data were abstracted. Thirteen patients with ACP were identified, which represented 0.8 percent of all pancreatic cancers diagnosed during the study period. Six of 13 patients had EUS. Features of these 6 tumors: median diameter of 42 mm (range, 20-100 mm), hypoechoic (n=6), solid (n=3) or mixed solid and cystic (n=3), heterogeneous (n=5) or homogeneous (n=1), and well defined (n=2) or poorly defined (n=4) borders. Five underwent EUS-FNA of a pancreatic mass, and cytology demonstrated ACP in 4 and ductal adenocarcinoma in 1. The diagnosis of ACP was confirmed after surgical resection in 2 of these 5, including one in whom cytology demonstrated only adenocarcinoma. The sixth patient had EUS without FNA, and surgical pathology after distal pancreatectomy found ACP. It was concluded that anaplastic carcinoma of the pancreas has variable endosonographic features. Endoscopic ultrasound-FNA may assist in the cytological diagnosis of these tumors [533].

Diagnostic delay

The prognosis of patients with pancreatic cancer remains poor despite recent advances in treatment. It is not known whether delays in referring, diagnosing and treating these patients and the way they present can affect their survival. In one study it was investigated the impact of clinical presentation (jaundice, abdominal pain, weight loss) and delays in management of these patients on their treatment and survival. Data on all patients with pancreatic cancer referred to a pancreatic unit (1997-2002) were collected prospectively. The delay in diagnosis and treatment for each patient was measured by estimating the time from the beginning of symptoms to the date of the referral letter (T1), the time from the referral date to the date of first review at the Unit (T2) and the time from date of review to the date of

diagnosis/treatment (T3). Treatments were defined as 1) pancreatic resections, 2) gastric and biliary bypass and 3) biliary stents. The term “operability” was used to describe patients thought to have a potentially removable tumour and had an operation and “resectability” applied to the patients whose tumour was actually removed at the operation. Follow-up time and survival were recorded by reviewing the patient's notes, hospital electronic databases and by contacting patients General Practitioners. There were a total of 355 patients with pancreatic cancer. Median age at diagnosis was 64 (i.q.r. 56-71) years and median follow-up was 8 (i.q.r. 4-14) months. The overall 1, 3 and 5 years patient's survival was 26 percent, 5 percent and 4 percent respectively. 1, 3 and 5 years survival of inoperable patients was 24 percent, 2 percent, and 0 percent and for operable patients was 35 percent, 13 percent, and 9 percent, respectively. The median survival time for those patients that underwent operation was significantly higher than those that did not (12 vs 6 months). The overall median time from initial symptoms to diagnosis/treatment (T1 + T2 + T3) was 102 (i.q.r. 56-182) days, T1 was 65 (i.q.r. 31-143), T2 17 (i.q.r. 8-28) and T3 11 (i.q.r. 6-21) days. The time delay from symptoms to referral (T1) had minimal clinical relevance to survival, with a hazard ratio of only 1.001 (95 % confidence interval 0.001 to 0.002) per day. Of all 355 patients, 305 (86 %) were reviewed and treated within 62 days from the GP referral (T2 + T3). There was no significant difference in operability, resectability and survival of patients that were diagnosed/treated before or after 62 days from referral (T2 + T3) (median months 7 and 8, respectively). Patients presenting with jaundice were referred (T1, median 56 vs 103) and diagnosed/treated (T2 + T3, median 96 vs 130) days) sooner, had a higher operability rate (33 % vs 21 %) but not a significantly higher resectability rate of (37 % vs 29 %). Isolated or combined mode of clinical presentation had no significant effect on survival. On multivariate regression analysis, prognostic factors of survival were a resectable tumour and the time from the beginning of symptoms to referral. The study showed that pre-hospital delays in referring patients to a specialist unit, but not hospital related 62 days target, had an no impact on operability, resectability and survival. Clinical presentation also had no impact on the survival. It was confirmed that pancreatic resection is the most important factor in determining the length of survival in patients with pancreatic cancer. The study implies that the successful implementation of the 62 days National Cancer Waits Target across the UK is unlikely to have an impact on prognosis in patients with pancreatic cancer. Focusing on early referral to specialist Pancreatic Units might be more effective [534].

Differential diagnosis

Intrapancreatic accessory spleen

Intrapancreatic accessory spleen (IPAS) is a congenital abnormality, which mimics neoplasm. Distinguishing IPAS from pancreatic neoplasm/malignancy is extremely important from a treatment perspective. It was reported a case of a 67-year-old asymptomatic man who had a 1.3-cm, incidentally detected, pancreatic tail mass. The mass was round, well-circumscribed, and hypervascular with uniform enhancement. The image findings were highly suggestive of a pancreatic endocrine neoplasm. An endoscopic ultrasound-guided fine-needle aspiration was performed. Conventional smears revealed a polymorphous population of lymphocytes admixed with a subset of other inflammatory cells. Hematoxylin-eosin–stained cell block sections showed conspicuous thin-walled blood vessels in addition to inflammatory cells. Immunostaining for CD8 demonstrated strong positivity in endothelial cells of the thin-walled vessels. By correlating the cytologic findings with the result of immunostaining, it was rendered the diagnosis of IPAS [535].

Choledochoceles

Choledochoceles have been classified as Todani Type III choledochal cysts. However, most surgical series of choledochal cysts have reported few choledochoceles because they are managed primarily by endoscopists. The aim of one analysis was to report a multidisciplinary series comparing choledochoceles to Todani Types I, II, IV, and V choledochal cysts. Surgical, endoscopic, and radiologic records were reviewed to identify patients with choledochal cysts. Patient demographics, presenting symptoms, radiologic studies, associated abnormalities, surgical and endoscopic procedures as well as outcomes were reviewed. A total of 146 patients with "choledochal cysts" including 45 children (31 %) and 28 with choledochoceles (18 %) were identified, which represents the largest Western series. Patients with choledochoceles were significantly older (51 vs 29 years) and significantly more likely to be male (43 % vs 19 %), to present with pancreatitis (48 % vs 24 %) rather than jaundice (11 % vs 30 %) or cholangitis (0 % vs 21 %), to have pancreas divisum (38 % vs 10 %), and to be managed with endoscopic therapy (79 % vs 17 %). Two patients with choledochoceles (7 %) had pancreatic neoplasms. It was concluded that patients with choledochoceles differ from patients with choledochal cysts with respect to age, gender, presentation, pancreatic ductal anatomy, and their management. The association between choledochoceles and pancreas divisum is a new observation. Therefore, it was concluded that classifications of choledochal cysts should not include choledochoceles [536].

Cholesterol crystal embolization

Cholesterol crystal embolization (CCE) can result in end-organ ischemia. A retrospective review of clinicopathologic data was performed. The first patient was anticoagulated with coumadin for chronic atrial fibrillation and presented subacutely with a solid mass. The second patient suffered from coronary artery disease post-angioplasty/stenting and presented with acute pancreatitis and pancreatic cystification. CCE should be considered in patients with significant vascular disease, arrhythmias or vascular manipulation who present with a pancreatic mass [537].

Differential diagnostic techniques

Analyses on sampled pancreatic juice

There is a need to develop methods of early diagnosis for pancreatic cancer. Pancreatic juice is easily collected by endoscopic retrograde cholangiopancreatography and may facilitate diagnosis using molecular markers. The aim of one work was to explore the feasibility of measurement of gene expression in RNA isolated from ductal juice. Intraoperative sampling of pancreatic juice was undertaken in 27 patients undergoing pancreaticoduodenectomy for suspected tumor. Total RNA was extracted and used as template for poly(adenylic acid)polymerase chain reaction (PCR) to generate a globally amplified complementary DNA pool representative of all expressed messenger RNAs. Real-time PCR was performed for trefoil factor 2 (TFF2), carboxypeptidase B1 (CPB1), and kallikrein-related peptidase 3 (KLK3) in a subset of samples; all samples were normalized for 3 reference genes (glyceraldehyde-3-phosphate dehydrogenase, GAPDH, PSMB6, and beta-2-microglobulin, B2M). The median volume of the pancreatic juice obtained was 1245 microL (range, 50-5000 microL). The RNA integrity number ranged from 1.9 to 10. Reverse transcriptase PCR was positive for pancreas-specific genes (TFF2 and CPB1) and negative for prostatic-specific antigen in all samples. These results demonstrate that RNA analysis of pancreatic juice is feasible using a combination of poly(A)-PCR and real-time PCR. In addition, the poly(A)-complementary DNA generated can be probed for multiple genes and is

indefinitely renewable, thereby representing a molecular block of importance for future research [538].

Laboratory diagnosis of ascites

Malignant ascites may be the first presentation of an unsuspected cancer. Pancreas and ovary are among the organs that are usually evaluated as a source of primary. The purpose of one study was to investigate a panel of immunohistochemical stains to help differentiate pancreatic from ovarian carcinoma. It was evaluated the immunohistochemical staining of eight commercially available antibodies MUC1, MUC2, MUC5ac, Wilm's tumor susceptibility gene 1 (WT1), cytokeratin 7 (CK7), CK20, CA125, and CA19.9 in 25 effusion specimens with evidence of metastatic carcinoma including 14 ovarian serous carcinomas, 9 pancreatic adenocarcinomas, and 2 unknown primaries. Primary ovarian serous carcinomas were positive for WT-1 (100 %), CK7 (93 %), CK20 (43 %), CA125 (100 %), CA19.9 (50 %), MUC1 (100 %), MUC2 (0 %), and MUC5ac (0 %). Primary pancreatic carcinomas were positive for MUC5ac (100 %), MUC1 (100 %), CA19.9 (100 %), CK7 (78 %), CK20 (22 %), CA125 (89 %), WT-1 (0 %), and MUC 2 (0 %). The combination of MUC5ac positivity/WT-1 negativity was seen in 100 percent of pancreatic carcinoma, whereas MUC5ac negativity/WT-1 positivity in 100 percent of ovarian serous carcinoma. It appears that the combination of MUC5ac and WT-1 stains is useful in distinguishing pancreatic ductal from ovarian serous carcinoma in body fluid cytology [539].

Circulating tumor cells

The quantification of circulating tumor cells has been historically problematic due to the different methods applied to their measurement. Following the development of standardized technology, they are now becoming well-established prognostic and predictive markers in patients with breast, colon and prostate cancer. While they represent a real-time noninvasive test, their use in diagnostics has seldom been reported. It was reported their use to help diagnose an indeterminate pancreatic mass. The use of an automated circulating tumor cell platform as described is likely to have utility as an aid to differential diagnosis, although larger studies will be required to ascertain its positive or negative predictive value [540].

Circulating DNA

Although patients with chronic pancreatitis (CP) have an increased risk of pancreatic cancer (PanCa), the timely detection of PanCa often is difficult, because the symptoms of CP and PanCa are very similar. Moreover, secondary inflammation may be identified in PanCa, further complicating diagnosis. To improve the survival of patients with PanCa, a reliable test to differentiate CP from PanCa is needed. In one article, the authors describe a methylation profile of cell-free plasma DNA that distinguished CP from PanCa with >90 percent accuracy. METHODS:: Methylation in cell-free, plasma DNA was compared among 30 samples from patients with CP, 30 samples from patients with PanCa, and 30 samples from healthy controls (N) using a microarray-mediated methylation analysis of 56 fragments in each sample (MethDet56). Statistical analysis was done by using the Fisher exact test, a naive Bayes algorithm, and 25 rounds of 5-fold cross-validation. The MethDet56 methylation analysis technique identified 17 gene promoters as informative (8 for distinguishing N from CP and 14 for distinguishing CP from PanCa). It achieved 82 percent sensitivity and 78 percent specificity in the detection of CP (N vs CP) and 91 percent sensitivity and 91 percent specificity in the differential detection of PanCa (PanCa vs CP). The current data suggested that, among patients with pancreatic disease, the methylation profiles of inflammatory disease and cancer are different and open a new venue for the development of biomarkers for differential diagnosis. Further investigation of diagnostic biomarkers for pancreatic cancer based on methylation in cell-free, circulating DNA appears to be warranted [541].

Peritoneal metastases

An optical probe, RG-(gal)(28)GSA, was synthesized to improve the detection of peritoneal implants by targeting the beta-d-galactose receptors highly expressed on the cell surface of a wide variety of cancers arising from the ovary, pancreas, colon, and stomach. Evaluation of RG-(gal)(28)GSA, RG-(gal)(20)GSA, glucose-analogue RG-(glu)(28)GSA, and control RG-HSA demonstrates specificity for the galactose, binding to several human adenocarcinoma cell lines, and cellular internalization. Studies using peritoneally disseminated SHIN3 xenografts in mice also confirmed a preference for galactose with the ability to detect submillimeter size lesions. Preliminary toxicity study for RG-(gal)(28)GSA using Balb/c mice reveal no toxic effects up to 100x of the standard imaging dose of 1 mg/kg administered either intraperitoneally or intravenously. These data indicate that RG-(gal)(28)GSA can selectively target a variety of human adenocarcinomas, can improve intraoperative or endoscopic tumor detection and resection, and may have little or no toxic in vivo effects; hence, it may be clinically translatable [542].

Venous thromboembolism

One paper was an updated review of a classical clinical subject: the association between deep vein thrombosis and pancreatic cancer. Recent epidemiological data support the empirical observation of Trousseau that digestive cancer may induce deep vein thrombosis. Pancreatic cancer is among the most common malignancies associated with thrombosis, due to the fact that cancer may induce the activation of the coagulation. There are genetic factors linked to this association. Cancer patients carrying the factor V Leiden mutation and the prothrombin 20210A mutation have increased risk to develop thrombosis. Reciprocally, it has been speculated that deep vein thrombosis or pulmonary embolism could represent a warning sign for a latent cancer. The practical question about this association is: shall we recommend searching for pancreatic and other cancers in all patients with thrombosis? Present data show that the strategy to look for such malignancies in patients with thrombosis on a routine base is not cost-effective. Oncological screening should be limited to patients at risk to develop cancer. Patients with pancreatic cancer, as with other visceral cancers, should be submitted to a prophylactic strategy to prevent thrombosis: therapy with low-molecular-weight heparin for several weeks was beneficial in several trials [543].

Platelet factor 4 (PF4) has been proposed as a diagnostic biomarker for PDAC. Serum PF4 levels were determined by enzyme-linked immunosorbent assay in an initial cohort of 62 PDAC patients, 62 healthy control subjects, and 34 chronic pancreatitis patients. A second validation set consisted of 71 PDAC patients. Linear regression models were used to relate PF4 to class, gender, age, stage, platelet count, and diagnosis. In the initial cohort, serum PF4 levels distinguished PDAC significantly from chronic pancreatitis patients, but not from healthy control subjects. In PDAC patients, high serum PF4 level significantly predicted decreased survival independent of all covariates examined. The prognostic relationship of serum PF4 levels remained significant in the validation set. Venous thromboembolism (VTE) occurred in 20 percent of the 133 PDAC patients. The VTE risk was higher in subjects with elevated PF4 levels. Serum PF4 is shown for the first time to be prognostic for survival in PDAC patients. High PF4 is associated with an increased risk for the development of VTE. Serum PF4 levels may therefore be useful for patient stratification and for directing treatment options in patients with pancreatic cancer including anticoagulation prophylaxis [544].

Venous thromboembolism (VTE) is associated with cancer. Cancer patient with thromboembolism have poorer prognosis. One study assessed the risk and mortality in pancreatic cancer patients who develop VTE. A retrospective chart review was performed of 201 patients with pancreatic cancer. VTE was observed in 58 (29 %) patients, 37/58 had

deep vein thrombosis (DVT), 11/58 pulmonary embolism and 10/58 had both. Twenty-six out of 107 patients with tumor of head of the pancreas developed VTE (24 %), compared to half of the patients with body of the pancreas involvement. Stage IV was defined in 99 patients, 39/99 had VTE (39 %). Median survival time was 15 months for patients without VTE compared to 13 months with VTE. It was concluded that patients with body of the pancreas and stage IV tumors had increased risk of developing VTE. There was no survival difference between patients with VTE compared to those without [545].

Venous thromboembolism (VTE) frequently complicates cancer. Data on tumour-specific VTE predictors are limited, but may inform strategies to prevent thrombosis. It was computed incidence rates (IRs) with 95 percent confidence intervals (CIs) for VTE hospitalisation in a cohort of cancer patients (n=57,591) and in a comparison general-population cohort (n=287,476) in Denmark. The subjects entered the study in 1997-2005, and the follow-up continued through 2006. Using Cox proportional-hazards regression, we estimated relative risks (RRs) for VTE predictors, while adjusting for comorbidity. Throughout the follow-up, VTE IR was higher among the cancer patients (IR=8.0, 95 % confidence interval 7.6 to 8.5) than the general population (IR=4.7, 95 % confidence interval 4.3 to 5.1), particularly in the first year after cancer diagnosis (IR=15.0, 95 % CI confidence interval 3.8 to 16.2, vs IR=8.6, 95 % confidence interval 7.6 to 9.9). Incidence rates of VTE were highest in patients with pancreas (IR=40.9, 95 % confidence interval 29.5 to 56.7), brain (IR=17.7, 95 % confidence interval 11.3 to 27.8) or liver (IR=20.4, 95 % confidence interval 9.2 to 45.3) tumours, multiple myeloma (IR=22.6, 95 % confidence interval 15.4 to 33.2) and among patients with advanced-stage cancers (IR=27.7, 95 % confidence interval 24.0 to 32.0) or those who received chemotherapy or no/symptomatic treatment. The adjusted RR (aRR) for VTE was highest among patients with pancreas (aRR=16.3, 95 % confidence interval 8.1 to 32.6) or brain cancer (aRR=19.8 95 % confidence interval 7.1 to 55.2), multiple myeloma (aRR=46.1, 95 % confidence interval 13.1 to 162.0) and among patients receiving chemotherapy, either alone (aRR=18.5, 95 % confidence interval 11.9 to 28.7) or in combination treatments (aRR=16.2, 95 % confidence interval 12.0 to 21.7). It was concluded that risk of VTE is significantly higher among cancer patients than in the general population. Predictors of VTE include recency of cancer diagnosis, cancer site, stage and the type of cancer-directed treatment [546].

Treatment options

Venous thromboembolism (VTE) is a frequent cause of morbidity and mortality in cancer patients. A significant proportion of cancer-associated VTE occurs in the ambulatory setting and is associated with poorer outcomes and reduced survival. Risk for VTE is influenced by patient, cancer and treatment-specific factors. Recent studies have identified biomarkers associated with increased VTE risk in malignancy, including leukocyte and platelet counts, tissue factor, prothrombin split products, D-dimer, P-selectin, factor VIII and C-reactive protein. Recent and ongoing clinical trials have focused on VTE prophylaxis with low-molecular weight heparins in high-risk cancer outpatients, particularly those with pancreatic cancer. These studies have yielded encouraging preliminary results but whether thromboprophylaxis provides significant benefit to unselected cancer outpatients remains unclear. A risk stratification model incorporating known risk factors and biomarkers can identify those patients at highest risk. This review focuses on emerging data regarding risk assessment and benefit of thromboprophylaxis in patients with cancer [547].

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continued through 2006. Using Cox proportional-hazards regression, it was estimated relative risks (RRs) for VTE predictors, while adjusting for comorbidity. Throughout the follow-up, VTE IR was significantly higher among the cancer patients (IR=8.0, 95 % confidence interval 7.6 to 8.5) than the general population (IR=4.7, 95 % confidence interval 4.3-5.1), particularly in the first year after cancer diagnosis (IR=15.0, 95 % confidence interval 13.8 to 16.2, vs IR=8.6, 95 % confidence interval 7.6 to 9.9). Incidence rates of VTE were highest in patients with pancreas (IR=40.9, 95 % confidence interval 29.5 to 56.7), brain or liver tumours, multiple myeloma and among patients with advanced-stage cancers or those who received chemotherapy or no/symptomatic treatment. The adjusted RR (aRR) for VTE was highest among patients with pancreas (aRR=16.3, 95 % confidence interval 8.1 to 32.6) or, multiple myeloma and among patients receiving chemotherapy, either alone or in combination treatments. It was concluded that the risk of VTE is higher among cancer patients than in the general population. Predictors of VTE include recency of cancer diagnosis, cancer site, stage and the type of cancer-directed treatment [548].

Portal vein thrombosis

To assess patients with chronic portal vein thrombosis (PVT) with respect to transcapsular collateral veins, the communication between these veins and ectopic varices, and the cause of PVT 145 consecutive patients with chronic PVT due to a variety of causes were assessed for transcapsular collaterals and ectopic varices with ultrasonography (US) from 2003 to 2008. Transcapsular collaterals were detected in 15 (10 %) of 145 patients with chronic PVT. They were restricted to patients with a history of hepatobiliary surgery, severe pancreatitis, or abdominal surgery (n=21) and were not detected in patients with liver cirrhosis, systemic coagulopathy, extrahepatic malignancy, idiopathic PVT, chronic pancreatitis, or infectious or inflammatory diseases (n=124). Ectopic varices were infrequent in 70 patients with liver cirrhosis (n=2, 3 %) but were common in 14 patients with PVT after hepatobiliary surgery (n=9, 64 %). Direct communication between transcapsular collaterals and ectopic varices was visible in all nine patients in this cohort. In eight of these patients, ectopic varices were found to be the bleeding source in gastrointestinal hemorrhage. Transcapsular collaterals frequently occur in patients with chronic PVT due to hepatobiliary surgery or necrotizing pancreatitis. They are associated with ectopic varices; therefore, awareness of transcapsular collaterals in this patient subgroup will help to localize ectopic varices as potential bleeding source [549].

Aspects of quality of life

The purpose of one paper was to analyze the social organization of caring as gendered work as it relates to meal preparation and consumption activities surrounding older adult cancer patients and their caregivers. It was used a qualitative method consisting of in-depth, semi-structured, face-to-face interviews with 30 older cancer patients (17 women and 13 men aged 68-90) and their caregivers were conducted separately. Participants were diagnosed with pancreatic, colon, breast, lymphoma, skin, and head and neck cancer. Major findings were that both patients and caregivers experienced distress surrounding food preparation and mealtime activities, and these varied according to the gender of both patients and caregivers and the relationship that existed between patients and caregivers. Of particular note, female patients experienced distress over not being able to fully participate in meal planning and cooking activities that were central to their self-identity. Related to this, male spouses experienced frustration over not being able to engage in cooking activities that met their wives' expectations. Female caregivers expressed tremendous discontent that the one they were caring for did not eat like they "should". Matters related to the organization of meals and food consumption activities may be a source of significant distress for patients

and caregivers. Further research and greater attention from health care providers are warranted to evaluate the extent of such distress [550].

PANCREATIC CANCER, SURGERY

Organisation of care

In the late nineties of the former century, surgery for pancreatic and peri-ampullary cancer in the southern part of The Netherlands was performed mainly in low-volume hospitals (<5 resections/year). Results reported by the Comprehensive Cancer Center South (CCCS) in 2005 revealed the clearly disappointing results of this practice. The former stimulated the regionalisation of pancreatic surgery by 3 collaborating surgical units into one non-academic teaching hospital in the eastern part of the CCCS-region starting from July 2005. All of the 76 patients in this regional cohort group in whom a resection of a (peri-)pancreatic tumour was performed with curative intent have been followed up prospectively. The results of surgical morbidity and in-hospital mortality were compared with the results of the CCCS cohort group which were reported previously. Ever since the regionalisation the annual number of patients undergoing resection of a pancreatic tumour increased from 10 to 33, resulting in a total number of 76 patients. Post-operative complications, reoperation rate and in-hospital mortality decreased significantly to 34 %, 18 % and 2.6 % respectively, as compared to 72 %, 38 % and 24 % in the time period before regionalisation (a statistical, human and economically significant difference). These unique comparative prospective data derived from daily practice in a collaborative surgical region in The Netherlands (CCCS) support the need for centralisation of pancreatic surgery in order to improve standard of care in pancreatic surgery. This can be achieved by collaboration in a large regional hospital [551].

Patients and payers wish to identify hospitals with good surgical oncology outcomes. The objective in one study was to determine whether differences in outcomes explained by hospital structural characteristics are mitigated by differences in patient severity. Using hospital administrative and cancer registry records in Pennsylvania, it was identified 24,618 adults hospitalized for cancer-related operations. Colorectal, prostate, endometrial, ovarian, head and neck, lung, esophageal, and pancreatic cancers were studied. Outcome measures were 30-day mortality and failure to rescue (FTR) (30-day mortality preceded by a complication). After severity of illness adjustment, it was estimated logistic regression models to predict the likelihood of both outcomes. In addition to American Hospital Association survey data, we externally verified hospitals with National Cancer Institute (NCI) cancer center or Commission on Cancer (COC) cancer program status. Patients in hospitals with NCI cancer centers were significantly younger and less acutely ill on admission. Patients in high volume hospitals were younger, had lower admission acuity, yet had more advanced cancer. Unadjusted 30-day mortality rates were significantly lower in NCI-designated hospitals (3.8 % vs 2.2 %). Risk-adjusted FTR rates were significantly lower in NCI-designated hospitals (4.9 % vs 3.5 %). NCI center designation was a significant predictor of 30-day mortality when considering patient and hospital characteristics (OR 0.68; 95 % confidence interval 0.47 to 0.97). It was not found significant outcomes effects based on COC cancer program approval and it was concluded that patient severity of illness varies significantly across hospitals, which may explain the outcome differences observed. Severity adjustment is crucial to understanding outcome differences. Outcomes were better than predicted for NCI-designated hospitals [552].

Studies have demonstrated volume-outcome relationships for numerous operations, providing an impetus for regionalization; however, volume-based regionalization may not be feasible or necessary. The objective of one study was to determine if low-risk patients undergoing surgery at Community Hospitals have perioperative mortality rates comparable with Specialized Centers. From the National Cancer Data Base, 940,718 patients from approximately 1430 hospitals were identified who underwent resection for 1 of 15 cancers (2003-2005). Patients were stratified by preoperative risk according to age and comorbidities.

Separately for each cancer, regression modeling stratified by high- and low-risk groups was used to compare 60-day mortality at Specialized Centers (National Cancer Institute-designated and/or highest-volume quintile institutions), Other Academic Institutions (lower-volume, non-National Cancer Institute), and Community Hospitals. Low-risk patients had statistically similar perioperative mortality rates at Specialized Centers and Community Hospitals for 13 of 15 operations. High-risk patients had significantly lower perioperative mortality rates at Specialized Centers compared with Community Hospitals for 9 of 15 cancers. Regardless of risk group, perioperative mortality rates were significantly lower for pancreatectomy and esophagectomy at Specialized Centers. Risk-based referral compared with volume-based regionalization of most patients would require fewer patients to change to Specialized Centers. The authors concluded that perioperative mortality for low-risk patients was comparable at Specialized Centers and Community Hospitals for all cancers except esophageal and pancreatic, thus questioning volume-based regionalization of all patients. Rather, only high-risk patients may need to change hospitals. Mortality rates could be reduced if factors at Specialized Centers resulting in better outcomes for high-risk patients can be identified and transferred to other hospitals [553].

Recently, hospital and surgeon volume is widely discussed as a prognostic factor after major pancreatic surgery. It was presented the experience regarding major pancreatectomy in a middle-volume center. During the last 11 years, 66 patients underwent major pancreatectomy (52 pancreaticoduodenectomy, 13 distal pancreatectomy with splenectomy, and one central pancreatectomy). Postoperative course and long-term outcome were recorded and analyzed. One patient died after pancreaticoduodenectomy for ampullary cancer (total mortality of approximately 1.5 % for the whole group of patients or 1.9 % for the group of patients who underwent pancreatoduodenectomy). None of the patients was reoperated on. Transient pancreatic fistula was observed in 46 patients (36 patients after pancreatoduodenectomy, 69 %, and 10 patients after distal pancreatectomy, 77 %). Two patients required percutaneous computed tomography-guided drainage of fluid collections, whereas in another one, a tube thoracostomy was performed to drain a pleuritic fluid collection. Delayed gastric emptying was observed in 6 patients after pancreatectomy. Median survival for the whole group of patients was 17 months [554].

Impact of socioeconomic factors on enrollment in trials

Pancreatic resection is being performed with increasing frequency and safety. Technical outcomes and long-term survival for neoplastic lesions are well reported; however, reasons why patients do not undergo surgery for potentially resectable lesions are not well understood. The aim of one study was to determine the factors contributing to the decision not to operate for resectable pancreatic neoplasms. From 2004 to 2008, all patients with resectable pancreatic neoplasms at a single high-volume hepatopancreaticobiliary center were evaluated. The impact of patient factors, sociodemographics, medical comorbidities (Charlson combined comorbidity index (CCI) and ACCI), disease factors (tumor characteristics), and surgical factors (type of resection required) on the decision to undergo pancreatectomy were analyzed using univariate and multivariate binary logistic regression analysis. Three hundred seventy-five patients with resectable pancreatic lesions were identified. The median age was 62 years (21-93); 203 out of 375 (54 %) were males. Fifty-five (15 %) did not undergo resection. On univariate analysis, age (odds ratio (OR) 1.12), non-English speaking background (NESB; OR 4.28), tumor type (increased for cystic neoplasms including intraductal papillary mucinous neoplasm), CCI score (OR 1.24), and ACCI score (OR 1.43) were associated with an increased risk of not undergoing resection. Gender, age, marital status, and urban residence were not predictive. On multivariate analysis, NESB and the ACCI remained predictive of not undergoing resection. The majority of patients did not undergo surgery because the patient declined in 25 out of 55 (46 %), and resection was not offered in 15 out of 55 (27 %). In the remainder, medical contraindications

precluded surgery. Advanced age, tumor type, comorbidities (27 %), age (22 %), surgical risk (29 %), frailty (18 %), and uncertain diagnosis (6 %) were cited as reasons for not proceeding with surgery. Patients with a higher ACCI and those from a non-English spoken background are less likely to undergo surgery for resectable neoplastic lesions of the pancreas. These factors must be taken into consideration in the decision-making process when considering surgery for patients with pancreatic neoplasms. Novel strategies should be employed to optimize access to surgery for patients with resectable pancreatic [555].

Over 18 years, 7 phase 2 trials in advanced pancreatic cancer (APC) were conducted at a cancer institute (KCI). It was looked for factors that influenced the selection of patients for clinical trials and explored differences in overall survival (OS) of patients treated on clinical trials versus standard of care. The target population was patients with APC diagnosed between 1986 and 2003. Patients were divided into 3 mutually exclusive groups: treated on clinical trials at KCI (t-KCI), treated at KCI but not on a clinical trial (KCI), or treated at non-KCI institutions (n-KCI). Eight thousand two hundred thirty patients met study criteria: 6470 n-KCI, 1642 KCI, and 118 t-KCI. Significant differences were observed across the 3 groups with respect to age, race, stage, grade, and socioeconomic status. Median OS was higher in t-KCI (9 months) than in KCI (5 months) or n-KCI (3 months) and could not be accounted for by variations in baseline characteristics. It was concluded that patients enrolled on clinical trials were younger, had better socioeconomic status, and were less often African American. Patients with APC treated at academic institutions may have longer OS than patients treated in the community. Clinical trials seem to offer a survival advantage for patients with APC [556].

Preoperative staging

Despite advances in preoperative staging, cancer of the pancreatic head is frequently found to be unresectable at laparotomy. It was therefore performed a retrospective institutional review of patients referred for resection of cancer of the pancreatic head over a 2-year period. The primary outcome was the rate of metastasis or unresectable disease found at laparotomy in patients who were booked for pancreaticoduodenectomy with curative intent. During the study period, 133 patients were referred with suspected cancer of the pancreatic head. All underwent preoperative computed tomography scanning. Twenty-four also underwent preoperative endoscopic ultrasonography (EUS) and 23 also underwent magnetic resonance imaging (MRI). In total, 78 patients were deemed not to be candidates for surgery, leaving 55 patients with potentially resectable cancer who were scheduled for pancreatoduodenectomy. Of these, 32 patients (58 %) underwent successful resection with curative intent, and 23 patients (42 %) were found to have metastatic or locally advanced disease not identified by preoperative staging. Reasons for nonresectability were metastases (9 patients, 16 %), vascular involvement (12 patients, 22 %) and mesentery involvement (2 patients, 4 %). One patient had a diagnostic laparoscopy immediately before planned open exploration and was found to have peritoneal seeding precluding curative resection. Of the patients who underwent EUS, 14 were not surgical candidates because of locally advanced tumours. Ten patients were offered surgery with curative intent, and 5 patients (50 %) were found have unresectable tumours (4 metastatic, 1 locally advanced). Of the patients who underwent MRI, 11 were offered surgery, and 5 (45 %) had unresectable tumours (2 metastatic, 3 locally advanced disease). It was concluded that preoperative staging for cancer of the pancreatic head misses a substantial number of metastatic and unresectable disease [557].

Predictors of survival

Overall survival

In patients with unresectable pancreatic cancer, estimation of individual prognosis is essential to provide the most suitable biliary stent (self-expanding metal stent or plastic stent). The aim of one study was to determine prognostic factors for survival in patients with unresectable pancreatic cancer after initial biliary drainage. The study included 278 patients with unresectable pancreatic cancer. Prognostic factors for survival were analyzed using the Cox proportional hazards model, the Kaplan-Meier survival estimator, and the Wilcoxon test for difference in survival. In univariate analysis, advanced T stage according to the TNM classification and the presence of distant metastases were predictive factors for shorter survival. However, in multivariate analysis, the presence of distant metastasis was the only independent prognostic factor. The median survival time after initial biliary drainage was 3 and 7 months in patients with and without the presence of distant metastases, respectively [558].

Socioeconomic factors

The aim of one study was to evaluate the impact of demographic factors (DGF) and socioeconomic status (SES) on survival after pancreatic cancer resection in a German setting. Patients with pancreatic adenocarcinoma and pancreaticoduodenectomy were identified from our pancreatic resection database (1989-2008). DGF, SES, survival and tumor-related information were obtained from hospital records, a registry office questionnaire, and telephone interviews with patients, relatives and general practitioners. Follow-up was completed in 117 patients. Median overall survival and 5-year survival rate was 22 month and 10 percent, respectively. Survival significantly improved over time with a 16 percent 5-year survival and a median survival of 27 month for recent patients. The longest survival period with a median of 63 month was observed for patients with AJCC stage I. Tumor-related factors and treatment period, but not SES influenced survival after pancreatic cancer resection in our cohort. It was concluded that disparities in survival among the patients depend solely on tumor-related factors and treatment period and could not be explained by SES including key factors like income or type of health insurance. The comparable postresection outcome of patients with low and high SES at our department could be in part due to the universal German multi-payer health system, based on compulsory enrolment for the majority, which seems not to support health care inequalities seen in other OECD countries [559].

Lymph node ratio

The objective of one study was to compare the prognostic significance of the lymph node ratio (LNR) with the absolute number of affected lymph nodes for resected pancreatic ductal adenocarcinoma. Data were collected from 84 patients who had undergone pancreatoduodenectomy for pancreatic ductal adenocarcinoma over a 10-year period. Patients were categorized into four groups according to the absolute LNR (0, 0-0.199, 0.2-0.299, ≥ 0.3). Kaplan-Meier and Cox proportional hazard models were used to evaluate the prognostic effect. An LNR of ≥ 0.2 (median survival 8 vs 36 months with LNR < 0.2) and ≥ 0.3 (median survival 6 vs 30 months with LNR < 0.3), tumor size, positive resection margin, and nodal involvement were found to be significant prognostic markers following univariate analysis. Following multivariate analysis, only LNR at both levels (≥ 0.2 ; HR 1.8, and LNR of ≥ 0.3 ; HR 2.7) were independent predictors of a poor outcome. The number of lymph nodes examined had no effect on overall survival in either node-positive patients or node-negative patients. It was concluded that the LNR represents a stronger independent prognostic

indicator than the absolute number of affected lymph nodes in patients with resected pancreatic ductal adenocarcinoma [560].

Transection line: R0 versus R1

The prognostic strength of R1 status increases with frequency of margin positivity and is enhanced by protocol driven pathology reporting. Currently, margins are treated uniformly with tumor at or close to any margin considered of equal prognostic significance. The resection involves a mobilization phase freeing the posterior margin and anterior surface then a transection phase requiring lympho-vascular division forming the medial resection and pancreatic transection margin. The comparative assessment of the relative importance of tumor involvement of these different margins has not previously been investigated. To determine the prognostic influence of residual tumor at or within 1 mm of the mobilization margins (R1Mobilization) compared with transection margins (R1Transection) following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma (PDAC) a retrospective analysis of 148 consecutive resections for PDAC from 1996-2007 was performed. The individual (pancreatic transection, medial, posterior, and anterior surface) margins were separately identified and analyzed by a senior pathologist. An R1 resection was defined as microscopic evidence of tumor ≤ 1 mm from a resection margin. R1Mobilization tumor extension included both R1Anterior and R1Posterior cases; while R1Transection included pancreatic neck/body transection, R1Medial and adjacent transection margins. R1 status was confirmed in 109 patients (74 %). The medial (46 %) and posterior (44 %) margins were most commonly involved. R1 status was found to be a significant independent predictor of poor outcome. R1Mobilization involvement only (n=48) was associated with a significantly longer median survival of 19 months (95 % confidence interval 14 to 25) versus 11 months (95 % confidence interval 7 to 15) for those with R1Transection tumor involvement (n=61). There was no significant difference in the survival of the R1Mobilization compared with R0 group. It was concluded that following pancreaticoduodenectomy for PDAC, involvement of the transection margins in contrast to mobilization margins defines a group whose outcome is significantly worse. This may impact upon the allocation of adjuvant therapy within the setting of randomized controlled trials [561].

The prognosis of patients with pancreatic cancer remains poor, even after potentially curative R0 resection. This discrepancy may be due to the histopathological misclassification of R1 cases as curative resections (R0) in the past. To test this hypothesis, color coding of all resection margins and organ surfaces as part of a standardized histopathological workup was implemented and prospectively tested on 100 pancreatic head specimens. Thirty-five patients were excluded from the analysis owing to the pathohistological diagnosis; only pancreatic ductal adenocarcinoma, distal bile duct adenocarcinoma, and periampullary adenocarcinoma were included. Applying the International Union Against Cancer criteria, 32 cancer resections were classified R0 (49 %), while 33 cases turned out to be R1 resections (51 %). The mesopancreas was infiltrated in 22 of the 33 R1 resection specimens (67 %). It proved to be the only site of tumor infiltration in 17 specimens (52 %). Applying the Royal College of Pathologists' criteria, 46 resections were classified R1 (71 %). As expected, the mesopancreas again was the most frequent site of noncurative resection (n=27; 59 %). It was concluded that using the intensified histopathological workup for pancreatic head cancer specimens resulted in an increased rate of R1 resections and the mesopancreas represents the primary site for positive resection margins. Such results are of relevance for patients' stratification in clinical trials [562].

Hardness of pancreatic remnant

One study reported the first results of durometrically measured hardness of human pancreas and investigates its correlation to palpatory determined hardness, grade of pancreatic

fibrosis, and preoperatively determined radiodensity. Fifty-two patients with pancreatic resections were prospectively recruited. Hardness of samples from pancreatic cancer, chronic pancreatitis, and normal pancreas was measured using a durometer on a 0-100 Shore units (SU) scale. Three pancreatic surgeons palpated the pancreas and reported their assessment of hardness on a subjective 0-100 "Bochum units" (BU) scale. Radiodensity and fibrosis of pancreatic tissue were used for comparison. Pancreatic hardness differed significantly in normal pancreas, chronic pancreatitis, and pancreatic cancer; 30 SU, 51 SU, and 66 SU, respectively. Palpatory hardness of normal pancreas was 20 BU and of pancreatitis 60 BU. It correlated well to durometric readings. Fibrosis grade and radiodensity correlated neither to durometry nor to palpation. Pancreatic leak developed 4/20 (20 %) patients with normal pancreas vs. 1/32 (3 %) with chronic pancreatitis in the resection margin. It was thus found that palpatory assessment of pancreatic hardness performed by experienced surgeons correlated well to durometric measurements and remains the method of choice for intraoperative decision making. Durometry was more precise and should be considered in studies on pancreatic texture and for teaching purposes. Hardness and fibrosis grade appeared to be independent characteristics of pancreatic texture [563].

Peritoneal lavage cytology

Peritoneal lavage cytology in the staging of pancreatic cancer is not widely used given improvements in computed tomography (CT). The aim of one study was to determine the utility of peritoneal lavage cytology in predicting survival in locally advanced pancreatic cancer. Between 2000 and 2008, 202 patients with biopsy-proven pancreatic cancer who were determined by pancreas protocol CT to be locally advanced and not currently resectable underwent diagnostic laparoscopy and peritoneal lavage for cytology (DL-PLC). DL-PLC upstaged 58 of 202 patients (29 %) to stage IV, who had a significantly worse median survival of 11 months versus 16 months. Positive cytology was an independent predictor of worse survival. Positive peritoneal cytology (stage IV disease) in locally advanced pancreatic cancer is common and predicts worse survival. This survival difference suggests that peritoneal cytology status might be useful in deciding treatment regimens in patients with locally advanced disease based on CT [564].

Preoperative bowel preparation

Mechanical bowel preparations (MBPs) are commonly administered preoperatively to patients who undergo pancreatoduodenectomy (PD); however, their effectiveness over a clear liquid diet (CLD) preparation remains unclear. The aim of one study was to determine whether MBP offers an advantage to patients who undergo PD. In a retrospective review, it was analyzed the clinical data from 100 consecutive PDs performed on patients who received preoperative MBP from 2006 to 2007, and we compared them with 100 consecutive patients who received a preoperative CLD from 2007 to 2008. No differences were observed between the MBP and CLD groups in the rates of pancreatic fistula (13 % vs 14 %), intra-abdominal abscess (11 % vs 13 %), or wound infection (9 % vs 8 %). Trends toward increased urinary tract infections (13 % vs 5 %) and *Clostridium difficile* infections were found in the MBP group (6 % vs 1 %). The median duration of postoperative hospital stay was 7 days in each group, and the 12-month survival rates were equivalent (74 % vs 75 %). It was concluded that there is no clinical benefit to the administration of a preoperative mechanical bowel preparation for patients undergoing pancreatoduodenectomy [565].

Preoperative biliary stenting

The benefits of preoperative biliary drainage, which was introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head, are unclear. In one multicenter, randomized trial, it was compared preoperative biliary drainage with surgery alone for patients with cancer of the pancreatic head. Patients with obstructive jaundice and a bilirubin level of 40 to 250 micromol per liter (2.3 to 14.6 mg per deciliter) were randomly assigned to undergo either preoperative biliary drainage for 4 to 6 weeks, followed by surgery, or surgery alone within 1 week after diagnosis. Preoperative biliary drainage was attempted primarily with the placement of an endoprosthesis by means of endoscopic retrograde cholangiopancreatography. The primary outcome was the rate of serious complications within 120 days after randomization. It was enrolled 202 patients; 96 were assigned to undergo early surgery and 106 to undergo preoperative biliary drainage; 6 patients were excluded from the analysis. The rates of serious complications were 39 percent (37 patients) in the early-surgery group and 74 percent (75 patients) in the biliary-drainage group (relative risk in the early-surgery group, 0.54; 95 % confidence interval 0.41 to 0.71), which was a significant difference. Preoperative biliary drainage was successful in 96 patients (94 %) after one or more attempts, with complications in 47 patients (46 %). Surgery-related complications occurred in 35 patients (37 %) in the early-surgery group and in 48 patients (47 %) in the biliary-drainage group (relative risk, 0.79; 95 % confidence interval 0.57 to 1.11), which was not a significant difference. Mortality and the length of hospital stay did not differ significantly between the two groups. It was concluded that routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications [566].

No conclusive evidence exists confirming the role of preoperative biliary drainage in reversing the physiological disturbances resulting from biliary obstruction to improve outcome. One review examined the impact of preoperative biliary drainage and the outcomes after surgery. A PubMed literature search was undertaken using the keywords preoperative, biliary, and drainage. The primary end points were the effect of preoperative biliary drainage on mortality, morbidity, and bile cultures. The secondary outcome measures were preoperative biliary drainage and pancreatic leakage, intra-abdominal abscess, sepsis/infectious complications, wound infection, hemorrhage, and bile leak rates. The impact of bile cultures positive for bacteria and the outcomes after surgery were also examined. Preoperative biliary drainage significantly increases wound and bile infection rates on meta-analysis using a fixed and random effect model, but no adverse effect on mortality and morbidity was found. A bile culture positive for bacteria negatively impacts on both mortality and morbidity after surgery. It was concluded that preoperative biliary drainage significantly increases the rates of bile culture positive for bacteria and the probability of wound infection. Bile cultures positive for bacteria adversely impact mortality and morbidity after surgery in jaundiced patients. Although no evidence has been found by this review that preoperative biliary drainage directly increases mortality and morbidity, it is possible that in certain patients, preoperative biliary drainage may deleteriously affect outcome by bacterial contamination of the bile [567].

Patients with obstructive jaundice due to pancreatic head cancer can undergo preoperative biliary drainage (PBD). The associated delay of surgery can lead to more advanced cancer stages at surgical exploration, affecting resection rate and survival. To evaluate the relation between delay in surgery because of preoperative biliary drainage (PBD) and survival in patients scheduled for surgery for pancreatic head cancer it was conducted a multicenter, randomized controlled clinical trial to compare PBD with early surgery (ES) for pancreatic head cancer for complications. Mean times from randomization to surgery were 1.2 (0.9-1.5) and 5.1 (4.8-5.5) weeks in the ES and PBD groups, respectively, which was a significant difference. In the ES group, 60 (67 %) of 89 patients underwent resection, versus 53 (58 %) of 91 patients in the PBD group. Median survival after randomization was 12.2 (9.1-15.4)

months in the ES group versus 12.7 (8.9-16.6) months in the PBD group. A longer time to surgery was significantly associated with slightly lower mortality rate after surgery (hazard ratio = 0.90, 95 % confidence interval 0.83 to 0.97), when taking into account resection, bilirubin, complications, pancreatic adenocarcinoma, tumor-positive lymph nodes, and microscopically residual disease. It was thus concluded that in patients with pancreatic head cancer, the delay in surgery associated with PBD does not impair or benefit survival rate [568].

The aim of this study was to evaluate the utility of intraoperative bile cultures on the outcome of patients undergoing pancreaticoduodenectomy. A review of a hepato-pancreato-biliary database was performed to identify all patients who had a pancreaticoduodenectomy from 1/1998 to 8/2008. Two hundred twenty-eight patients were evaluated, with preoperative biliary stenting performed in 129 out of 229 patients (57 %), with 63/129(49 %) had bile cultures taken intraoperatively, 39/129 (30 %) having positive bile cultures. Neither preoperative biliary stenting (incidence of complication: 54 % with stent vs 51 % without) nor positive bile culture (incidence of complication: 54 % with positive bile culture vs 53 % without) were predictors of overall complications. Length of operating time, length of hospital stay, blood loss, blood transfusion, and severity of complications were similar in the group with and without stent. There were 19 different organisms identified with not a single species was a statistically significant predictor of neither severity of complication nor increased length of stay. Preoperative biliary stenting correlates with similar rate of biliary infections, however, intraoperative bile culture allows for early appropriate antibiotic use, which maintains a similar morbidity and infectious incidence as in patients without stents [569].

Staging laparoscopy

Staging laparoscopy (SL) may prevent non-therapeutic laparotomy in patients with otherwise resectable pancreatico-biliary cancers, but evidence is inconclusive. One meta-analysis aimed to ascertain the true benefit of SL. All studies undertaking SL as a diagnostic sieve were included and data homogenised. Standard meta-analytical tools with emphasis on sensitivity testing and meta-regression to detect the cause for heterogeneity between studies were used. Twenty-nine studies satisfied the criteria; 3305 patients underwent SL of which 12 were incomplete. Morbidity (n=15) and mortality (n=1) was low. True yield of SL for pancreatic/peripancreatic cancers (PPC) was 25 percent (95 % confidence interval 24 to 27) with a diagnostic odds ratio (DOR) of 104 (95 % confidence interval 48 to 227). Resection rate improved from 61 percent to 80 percent. For proximal biliary cancers (PBC), SL increased the curative resection rate from 27 percent to 50 percent, with true yield of 47 percent and a DOR 61. Sub-group analysis for detection of liver and peritoneal lesions demonstrated a sensitivity of 88 percent (95 % confidence interval 83 to 92) and 92 percent (95 % confidence interval 84 to 96) for PPC; 83 percent (95 % confidence interval 69 to 92) and 93 percent (95 % confidence interval 81 to 99) for PBC, respectively. There was no between-study heterogeneity for peritoneal lesions. However for detection of local invasion, sensitivity was low: 58 percent (95 % confidence interval 51 to 65) for PPC and only 34 percent (95 % confidence interval 22 to 47) for PBC. Meta-regression did not reveal any cause for the observed heterogeneity between studies. It was concluded that staging laparoscopy offers significant benefit to patients with resectable pancreatico-biliary cancers in avoiding non-therapeutic laparotomy and should be adopted in routine clinical practice in a judicious algorithm [570].

Emergency pancreatoduodenectomy

Pancreaticoduodenectomy is a demanding procedure even in selected patients but becomes formidable when performed in cases of emergency. One study analyzed the experience with urgent pancreatoduodenectomies; special emphases were put on the evaluation of diagnostic means and the validation of existing indications for performance of this procedure. Three hundred one patients who underwent pancreatoduodenectomy between 1989 and 2008 were identified from a pancreatic resection database and reviewed for emergency indications. Six patients (2 %) underwent emergency pancreatoduodenectomy. Indications included endoscopy-related perforation, postoperative complications, and uncontrollable intraduodenal tumor bleeding. Length of stay and occurrence of nonsurgical complications were increased in emergency compared with elective pancreatoduodenectomies. Although increased, no significant differences were found regarding mortality and surgery-related complications. It was concluded that the indications for emergency pancreatoduodenectomies were based on clinical decisions rather than on radiologic diagnostics. Urgent pancreatic head resections may be considered as an option in selected patients if handling of local complications by interventional measures or limited surgery seems unsafe [571].

Classification of pancreatico-enteric anastomoses

To date, there is no uniform and standardized manner of defining pancreatic anastomoses after pancreatic resection. Therefore, a systematic search was performed to determine the various factors, either related to the pancreatic remnant after pancreatic resection or to types of pancreaticoenteric anastomoses that have been shown to influence failure rates of pancreatic anastomoses. Based on the data obtained, it was formulated a new classification that incorporates factors related to the pancreatic remnant, such as pancreatic duct size, length of mobilization, and gland texture, as well as factors related to the pancreaticoenteric anastomosis, such as the use of pancreaticojejunostomy/pancreatogastrostomy; duct-to-mucosa anastomosis; invagination (dunking) of the remnant into the jejunum or stomach; and the use of a stent (internal or external) across the anastomosis. By creating a standardized classification for recording and reporting of the pancreaticoenterostomy, future publications would allow a more objective comparison of outcomes after pancreatic surgery. In addition, use of such a classification might encourage studies evaluating outcomes after specific types of anastomoses in certain clinical situations that could lead to the formulation of best practice guidelines of anastomotic techniques for a particular combination of findings in the pancreatic remnant [572].

Operative technique: use of microscopy

It has been observed that leakage from pancreaticojejunostomy is reduced when a surgical microscope is used to construct the pancreaticojejunostomy during pancreaticoduodenectomy. To validate a hypothesis that better vision improves the technical performance of pancreaticojejunostomy, it was limited inclusion criteria to those patients at high risk for leak, performed more cases, and used the grading system of the International Study Group of Pancreatic Surgery. From 1988 through 2008, 507 consecutive pancreaticoduodenectomies were performed with pancreaticojejunostomy. A subset of 283 patients at risk for leak had a main pancreatic duct (MPD) ≤ 3 mm at the surgical margin. Pancreaticojejunostomy was completed with surgical loupes (n=135) or surgical microscope (n=148). Incidence of pancreaticojejunostomy leak and delayed gastric emptying was determined using a Web-based calculator for the severity grading scale of the International Study Group of Pancreatic Surgery. Within the 507 pancreaticoduodenectomies, the clinically relevant pancreaticojejunostomy leak for those with an MPD >3 mm (n=224) was 4 percent, and with an MPD ≤ 3

mm (n = 283) it was 16% (p < 0.0001). For these 283 high-risk patients, outcomes were significantly worse in the loupes versus microscope group, i.e. clinically relevant pancreaticojejunostomy leak (21 % vs 11 %), pancreas-related complications (31 % vs 19 %), clinically relevant delayed gastric emptying (19 % vs 9 %), and hospital length of stay (13 vs 10 days). It was concluded that in a subset of pancreaticoduodenectomy patients at high risk for pancreaticojejunostomy leak, the increased visual acuity of the surgical microscope reduced clinically relevant pancreatic anastomotic failure, delayed gastric emptying, and hospital length of stay [573].

Pancreatojejunostomy

Pancreatic fistula (PF) is the most important complication after pancreaticoduodenectomy. Recently, a zero percent rate of PF was reported using a binding pancreaticojejunostomy with intussusception of the pancreatic stump. The aim of one study was to assess the safety of this new binding pancreaticojejunostomy in condition most susceptible to PF, i.e. soft pancreas and non-dilated main pancreatic duct. Forty-five consecutive patients with soft pancreas and non-dilated main pancreatic duct underwent a binding pancreaticojejunostomy. Post-operative PF was defined according to the International Study Group of Pancreatic Fistula. Four patients (9 %) developed a PF. In one case, PF developed on post-operative day 3 due to a technical deficiency. In the three other cases, pancreatic fistula developed after the tenth post-operative day; all the patients had local and/or general co-morbidities before PF occurrence. It was concluded that binding pancreaticojejunostomy according to Peng is a safe and secure technique that improves the rate of pancreatic fistula, especially in case of soft texture of the pancreas remnant. However, a zero rate seems to be hard to achieve because other abdominal and general complications are frequent and can lead to secondary leakage of the pancreatic anastomosis [574].

Pancreaticoduodenectomy (PD) is the standard of care in the treatment of premalignant and malignant diseases of the head of the pancreas. Variability exists in anastomosis with the pancreatic remnant. One work described a safe and easy modification for the pancreatic anastomosis after PD. Ten patients underwent the "Whip-Stow" procedure for the management of the pancreatic remnant. PD combined with a Puestow (lateral pancreaticojejunostomy, LPJ) was completed using a running single-layer, 4-0 Prolene obeying a duct-to-mucosa technique. LPJ and pancreaticogastrostomy (PG) historical leak rates are reported to be 13.9 and 15.8 percent, respectively. Mortality, leak, and postoperative bleeding rates were 0 per cent in all patients. The Whip-Stow was completed without loops or microscope with a 4-0 single-layer suture decreasing the time and complexity of the anastomosis. Average time was 12 minutes as compared with the 50 minutes of a 5 or 6-0 interrupted, multilayered duct-mucosa anastomosis. Benefits included a long-segment LPJ. In this study, the Whip-Stow procedure was proven to be a safe and simple approach to pancreatic anastomosis in selected patients. This new technique provides the benefit of technical ease while obeying the age old principles of obtaining a wide duct to mucosa anastomosis [575].

Both patient-derived and technical factors contribute to pancreatic anastomotic failure. From a technical standpoint, an "ideal" pancreaticojejunal anastomosis would meet the following criteria:

- applicable to all patients
- easy to teach
- associated with a low rate of pancreatic anastomotic failure-related complications.

The pancreaticojejunostomy described by L Blumgart meets the criteria for an "ideal" pancreaticojejunostomy. It was performed an audit of results of a consecutive series of patients at two institutions who underwent pancreaticojejunostomy using the described technique. Pancreaticojejunostomy after pancreaticoduodenectomy was performed in all cases using a novel two-layer technique consisting of an outer full thickness pancreas-to-seromuscular jejunal anastomosis and an inner duct-to-mucosal anastomosis. Incidences of pancreatic anastomotic failure (measured using the International Study Group of Pancreatic Fistula definition) and perioperative pancreatic anastomotic failure-related complications were analyzed in 187 patients who underwent pancreaticojejunostomy after pancreaticoduodenectomy using the described technique. Overall mortality was 1.6 percent. The rate of clinically significant pancreatic anastomotic failure (International Study Group of Pancreatic Fistula grade B or C) was only 6.9 percent. There was no bleeding, reoperation, or mortality secondary to pancreatic anastomotic failure among patients in this series. The novel pancreaticojejunostomy is applicable to all patients in whom the pancreatic duct can be identified, and it is associated with very low rates of significant postoperative morbidity and mortality. These findings support its routine use for pancreaticojejunal reconstruction after pancreaticoduodenectomy [576].

Enforcement of pancreaticojejunostomy

To examine whether pressure-tight reinforcement of pancreaticojejunostomy (PJ) using polyglycolic acid (PGA) mesh and fibrin glue sealant can reduce the incidence of postoperative pancreatic fistula (POPF) a study population included 128 consecutive patients who underwent pancreaticoduodenectomy between 2006 and 2010. Postoperative mortality and morbidity among 50 patients who underwent reinforcement of PJ anastomosis using PGA mesh and fibrin glue were compared with 78 patients (historical controls). The 2 groups demonstrated no significant differences in frequencies of overall or septic complications, reoperation, or in-hospital death. No significant difference in the frequency of POPF, delayed gastric emptying, or intra-abdominal abscess was found between groups. There was no difference between the 2 groups in the number of necessary interventions, and no bleeding complications or POPF-related mortality occurred. The median length of postoperative in-hospital stay between the 2 groups was similar: 13 days (range, 8-101 days) versus 14 days (range, 8-61 days). Similar findings were observed in a subgroup analysis consisting of patients with a pancreatic duct diameter smaller than 3 mm. This retrospective single-center study thus showed that reinforcement of PJ anastomosis using PGA mesh and fibrin glue provided no significant benefit in reducing the frequency of POPF [577].

Transanastomotic ductal stents

Despite strategies aimed at reducing a postoperative pancreatic fistula (POPF) after pancreatectomies, the overall incidence remains unchanged. One such procedure, until now incompletely explored, is transanastomotic pancreatic (TAP) ductal stenting. It was conducted a systematic search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1983-2008 to determine if TAP ductal stents provide any benefit and, if so, in which clinical scenarios they can be recommended. Stents can be internal or external, intraoperative only, or temporary (several days). One randomized trial on internal stents across pancreaticojejunostomy (PJ) suggested a higher POPF rate in the stented group. One nonrandomized study using an internal stent for pancreaticogastrostomy (PG) revealed a 0 percent POPF rate. Results from studies where external stents were used across PJ/PG reported a lower incidence of POPF. No statistically significant difference was reported in a POPF incidence when internal stents were compared with externalized stents. Available data suggest improved outcomes of pancreatoenteric anastomosis when TAP ductal stent is inserted in small ducts (≤ 3 mm). It was concluded that there is insufficient evidence to support or refute improved outcomes after TAP ductal stent insertion in patients with PJ/PG with small ducts (≤ 3 mm) or soft pancreata. More evidence of benefit is needed before use of external stents can be recommended [578].

After standardization of the perioperative management of pancreaticoduodenectomy, it was retrospectively compared results in nonstented pancreaticojejunostomy with external-stented pancreaticojejunostomy. The study population included 129 consecutive patients who underwent pancreaticoduodenectomy between 2004 and 2008. The postoperative mortality and morbidity were compared between 51 patients with restrictive use of external stenting (group A) and 78 patients without external stenting (group B). The patient with a pancreatic duct of less than 3 mm in diameter was 31 percent in group A and 46 percent in group B. There were no differences in postoperative morbidity and mortality between the two groups. Although the frequency of overall postoperative pancreatic fistula development was significantly higher in group B than in group A (44 % vs 27 %), there was no difference in grade B/C postoperative pancreatic fistula rate. The length of in-hospital stay in group B was significantly shorter than group A (13 vs 24 days). There were no differences in postoperative morbidity and mortality between subgroups that were consisted of patients with small pancreatic duct diameter. The authors concluded that this retrospective single-center study showed that nonstented duct-to-mucosa anastomosis was a safe procedure and was associated with a shortened in-hospital stay [579].

It was prospectively investigated the efficacy of an external pancreatic duct stent to prevent pancreatic fistula in the nonfibrotic pancreas after pancreaticojejunostomy, in which the degree of pancreatic fibrosis was assessed objectively by using dynamic magnetic resonance imaging (MRI). Among the 67 consecutive patients who underwent pancreatic head resection, 45 patients were judged to have a normal pancreas without fibrosis based on the preoperative assessment of pancreatic fibrosis based on MRI. The patients were randomly allocated to 1 of 2 groups with (n=23) or without (n=22) use of an external pancreatic duct stent in performing a pancreaticojejunostomy. Pancreatic fistula developed in 8 (35 %) patients in the stented group: 3 grade A and 5 grade B; whereas in the nonstented group, 9 (41 %) patients developed pancreatic fistula: 3 grade A and 6 grade B. There were no significant differences in the incidence or severity of pancreatic fistula between the 2 groups. It was concluded that the utility of the external pancreatic duct stent after pancreaticojejunostomy was not found in the nonfibrotic pancreases, which were sorted according to the degree of pancreatic fibrosis using the pancreatic time-signal intensity curve analysis from MRI [580].

Infracolic pancreatoduodenectomy

Tumours arising from the head of the pancreas can invade both the proximal transverse colon and its mesocolon. At laparoscopy, this may be considered a contraindication to proceeding to pancreatoduodenectomy. However, in some patients, pancreatoduodenectomy can still be performed with an R0 resection using an en-bloc resection technique by an infracolic approach. This technique relies on the infracolic control of the superior mesenteric vein (SMV) and is based on the presence of a normal fat cuff around the superior mesenteric artery (SMA) on pre-operative imaging. The dissection is maintained along the adventitial plane of the SMA. Pancreatoduodenectomy is performed in conjunction with en-bloc resection of the transverse colon. In the event of tumour invading the SMV, this is also resected en-bloc with the pancreatic head and transverse colon. It was reviewed all such cases performed at our institution between 2004 and 2009. This technique was attempted in eleven patients. In two patients, the procedure had to be abandoned because of unexpected SMA encasement by tumour. In the remaining nine patients this procedure was carried out successfully. In the paper, the infracolic approach to pancreatoduodenectomy, and the associated limitations are described in detail. The authors concluded that the infracolic technique may be used to deal with large pancreatic head tumours and all pancreatic surgeons should be familiar with this technique. In the absence of metastatic

disease, large pancreatic head tumours involving the colon can be resected en-bloc with the pancreatic head, as long as the SMA is not encased by the tumour [581].

Organ preserving pancreatectomy

The clinical usefulness of organ-preserving pancreatectomy is not well established due to technical difficulty and ambiguity of functional merit. The purpose of this study is to evaluate the clinical efficacy of organ-preserving pancreatectomy such as duodenum-preserving resection of the head of the pancreas (DPRHP), pancreatic head resection with segmental duodenectomy (PHRSD), central pancreatectomy (CP) and spleen-preserving distal pancreatectomy (SPDP). Between 1995 and 2007, the DPRHP were performed in 14 patients, the PHRSD in 16 patients, the CP in 13 patients, and the SPDP in 45 patients for preoperatively diagnosed benign lesions or tumors with low-grade malignant potential. The clinical outcomes including surgical details, postoperative complications and long-term functional outcomes were compared between organ-preserving pancreatectomy and conventional pancreatectomy group. Major postoperative complications constituted the following: bile duct stricture in 7 percent in DPRHP, delayed gastric emptying in 31 percent in PHRSD, pancreatic fistula in 21 percent in CP. There were no significant differences in postoperative complications and long-term functional outcomes between two groups. Organ-preserving pancreatectomy is associated with tolerable postoperative complications, and good long-term outcome comparing to conventional pancreatectomy. Organ-preserving pancreatectomy could be alternative treatment for benign or low-grade malignant potential lesion of the pancreas or ampullary/parapapillary duodenum [582].

Middle pancreatectomy

To determine short-term outcomes following middle pancreatectomy with transgastric pancreaticogastric anastomosis a retrospective analysis of 23 patients who underwent middle pancreatectomy with transgastric pancreaticogastric anastomosis from 2005 through 2009 was performed. Indications for procedure, operative time, length of stay, morbidity, mortality, and need for readmission, antibiotics, reoperation, additional procedures, or transfusion were reviewed. The mean age of 15 women and 8 men who underwent middle pancreatectomy with transgastric pancreaticogastric anastomosis was 55 years. The median follow-up time was 13 months. The most commonly resected tumors were intraductal papillary mucinous neoplasms (n=9), serous cystadenomas (n= 5), and neuroendocrine tumors (n=4). The mean operative time was 191 ± 39 minutes. No patients required intraoperative transfusion. The median hospital stay was 5 days. The most common complications were pancreatic fistula (n=6), intra-abdominal abscess (n=4), and superficial skin infection (n=4). Three patients had splenic artery pseudoaneurysms. Seven patients required readmission; 2 required reoperation. No patients developed postoperative new or worsening endocrine or exocrine insufficiency. There were no deaths. It was concluded that middle pancreatectomy with transgastric pancreaticogastric anastomosis offers a safe alternative to the traditional Roux-en-Y pancreaticojejunostomy and may be technically simpler [583].

Middle pancreatectomy is infrequently performed in selected patients. The rationale is to preserve pancreatic function. One study evaluated the technique, operative outcomes, and long-term exocrine and endocrine pancreatic function of the middle pancreatectomy procedure. Nineteen patients who underwent middle pancreatectomy between 1996 and 2008 were reviewed. Indications included eight intraductal papillary-mucinous neoplasms, five endocrine tumors, one serous and two mucinous cystadenomas, and three other benign lesions. Reconstruction of the distal pancreatic remnant was performed with pancreaticogastrostomy using the duct-to-mucosa method in 16 patients and with Roux-en-Y

end-to-end pancreaticojejunostomy in three patients. Median operative time was 215 min. Perioperative mortality was nil. Morbidity was 53 percent, including 9 (47 %) pancreatic fistulas. One patient with hemorrhage, complicated by a pancreatic fistula was successfully treated by endovascular embolization. No patients required postsurgical reoperation. Only one patient had clinical exocrine insufficiency requiring pancreatic enzyme supplementation. None developed postresection new-onset insulin-dependent diabetes. It was concluded that middle pancreatectomy with pancreaticogastrostomy is feasible and reasonable technique. Although the incidence of pancreatic fistula formation may still be higher compared to conventional resection, long-term exocrine, and endocrine pancreatic function may be preserved. Thus, careful patient selection and experienced pancreatic surgeons in high-volume centers are of great importance [584].

Pancreaticoduodenectomy and distal pancreatectomy for lesions of the neck or body of the pancreas sacrifice a large amount of normal pancreatic tissue. Middle pancreatectomy (MP) is a parenchyma sparing technique that reduces the risk of postoperative endocrine and exocrine insufficiency. One study aimed to evaluate the perioperative and long-term results of MP and to clarify whether MP can be performed with outcomes comparable with traditional pancreatectomies. Twenty-six patients who underwent MP for benign or low-grade malignant tumor of the pancreas between 1991 and 2006 were identified. Their outcomes were compared with two separate control groups, 35 left-side pancreatectomies (LSP) and 60 right-side pancreatectomies (RSP). The mean operating time of the MP group was 295 minutes, which was significantly shorter than that for RSP. The rate of pancreatic fistula formation was higher in the MP group than in the two control groups, although the differences did not reach statistical significance. After a mean follow-up of 71 months, postoperative endocrine function was equivalent to the pre-operative values in the MP group, and none of the patients developed diabetes mellitus postoperatively. Only one patient in the MP group required enzyme substitution postoperatively for exocrine insufficiency. The MP group was inclined to be superior to the other two control groups in terms of postoperative nutritional status. Middle pancreatectomy is a reasonable technique that is indicated for selected patients with benign or low malignant tumors in the neck and body of the pancreas [585].

Pylorus-preserving pancreatoduodenectomy

Pancreaticoduodenectomy (PD) is the standard surgical treatment for resectable periampullary tumors. It can be performed with or without pylorus preservation. Many surgeons have a negative opinion of pylorus preserving PD (PPPD) and consider it an inferior operation, especially from an oncological point of view. One article reviewed the various aspects of PD in the context of operative factors like blood loss and operation time, complications such as delayed gastric emptying and anastomotic leaks, and the impact on quality of life and survival. It was aimed to show that PPPD is at least as good as classic PD, if not better in some aspects [586].

No-touch isolation technique

Because surgeons usually grasp tumors during pancreatoduodenectomy, this procedure may increase the risk of squeezing and shedding the cancer cells into the portal vein, retroperitoneum, and/or peritoneal cavity. In an effort to overcome these problems, It has been developed a surgical technique for no-touch pancreatoduodenectomy. From 2005 through 2008, 42 patients have been operated on following this technique. Resected margins were microscopically analyzed. It is resected cancers with wrapping them within Gerota's fascia and transect the retroperitoneal margin along the right surface of the superior

mesenteric artery and abdominal aorta without grasping tumors. In summary the no-touch pancreatoduodenectomy has many potential advantages that merit further investigation in future randomized controlled trials [587].

Arterial resection

Arterial resection (AR) has traditionally been considered as a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma. The objective of one study was to evaluate if pancreatic resection with AR was worthwhile. Between 1990 and 2008 the records of 26 consecutive patients who underwent a curative-intent pancreatic resection for adenocarcinoma of the pancreas with AR (AR+ group) were matched 1:1 to those of the whole series of pancreatic resection performed in our institution. The final study population (n=52) included two groups of patients: the study group AR+ (n=26) and the control group AR- (n=26). The 1- and 3-year survival rates were similar in the two groups (66 % and 22 %, median 17 months for the group AR+, versus 50 % and 18 %, median 12 months, for the group AR-). The multivariate analysis showed that: arterial wall invasion at the site of AR, the total number of resected lymph nodes of ≤ 15 , and perineural invasion were independent prognostic factors for survival. It was concluded that pancreatic resections with AR for adenocarcinoma allowed to obtain a 3-year survival rate similar to that of a matched group of patients not requiring AR [588].

Operative blood loss

Operative blood loss (OBL) has previously been shown to significantly predict shorter disease-specific survival (DSS) in patients undergoing various pancreatic operations for pancreatic cancer. It was now shown that OBL greater than 2000 mL is significantly associated with worse DSS on multivariate analysis (MVA) after controlling for other clinical, perioperative, and histopathologic factors. It may be estimated that less than 10 percent of resections have blood loss that exceeds 1000 mL in a high volume center. In conclusion, there is consistent evidence that OBL predicts a worse survival in patients undergoing surgery for pancreatic cancer. A risk stratification system to predict cancer-related death may be based on this [589].

The aim of one study was to determine the prognostic factors and assess the impact of excessive operative blood loss (OBL) on survival after pancreatectomy for invasive ductal adenocarcinoma. From the retrospective analysis, 271 patients were eligible for evaluation. Overall survival was assessed to clarify the prognostic determinants, including patient characteristics, perioperative factors, and tumor characteristics. The overall survival was significantly affected by the amount of OBL. The median survival times were 26, 15, and 9 months for OBL less than 1000, 1000 to 2000, and greater than 2000 mL, respectively. Operative blood loss greater than 2000 mL remained an independent prognostic factor in multivariate analysis. Operative blood loss of 2010 mL was found to be an appropriate cutoff level to predict early mortality within 6 months after resection (sensitivity, 0.660; specificity, 0.739). Male sex, year of resection, and plexus invasion were independently associated with OBL greater than 2000 mL. It was concluded that Excessive OBL was found to be a prognostic determinant of survival after surgery for pancreatic cancer. Operative blood loss can be used to stratify the risk for pancreatic cancer mortality. Successful curative resection with limited blood loss can contribute to improved survival [590].

Resection of pancreatic liver metastases

The management of patients with peri-ampullary liver metastasis remains controversial. It was sought to assess the safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. Between 1993 and 2009, 40 patients underwent curative intent surgery (resection and/or radiofrequency ablation (RFA)) for peri-ampullary liver metastasis. Location of the primary tumor was pancreas head (n=20), ampulla of Vater (n=10), distal bile duct (n=5), or duodenum (n=5). Most patients (n=27) presented with synchronous disease, while 13 patients presented with metachronous disease following a median disease-free interval of 22 months. Most patients (n=25) presented with hepatic metastasis from pancreaticobiliary origin (pancreatic or distal common bile duct) compared with 15 patients who had metastasis from an intestinal-type primary (ampullary or duodenal). There were no differences in metastatic tumor number or size between these groups. Post-operative morbidity and mortality was 30 percent and 5 percent respectively. Overall 1- and 3-year survival was 55 percent and 18 percent. Patients who underwent resection of liver metastasis from intestinal-type tumors experienced a significant longer survival compared with patients who had pancreaticobiliary lesions (median: 13 months vs 23 months). It was concluded that curative intent surgery for peri-ampullary liver metastasis was associated with post-operative morbidity and a 5 percent mortality rate. Although the overall survival benefit was modest, patients with liver metastasis from intestinal-type tumors experienced improved survival following resection of liver metastasis compared with pancreaticobiliary lesions [591].

Combined liver and pancreatic resection

Combined resection of both the liver and pancreas for malignancy remains a controversial procedure. To many, the need for such an extended procedure implies an extent of disease that is usually not amenable to surgical control, and the extent of the procedure exposes the patients to substantial operative risks. The purpose of one study was to assess the results with combined resection of the liver and pancreas. Forty patients underwent combined liver and pancreas resection from 1996 to 2009. Patient ages ranged from 39 to 69 years (mean 53 years). Underlying diagnoses were neuroendocrine tumor (13), cholangiocarcinoma (13), gallbladder carcinoma (9), gastrointestinal stromal tumor (3), colorectal cancer (1), and metastatic ocular melanoma (1). Pancreatic resections included 26 pancreateoduodenectomies (PD) and 14 distal pancreatic resections. Liver resections included 18 trisectionectomies (13 right, 5 left), 10 lobectomies (8 right, 2 left), and 12 segmental resections. There was no perioperative mortality. One patient who underwent PD with right trisegmentectomy for gallbladder cancer developed postoperative liver failure that improved with supportive management. Two patients developed bile leaks that resolved with conservative management. One patient developed a pancreatic leak/hemorrhage and required a completion pancreatectomy. Mean hospital stay was 14 days (range 7 to 42 days). Median follow-up was 30 months (range 3 to 76 months). Patients undergoing resection for neuroendocrine tumors had a better 5-year survival than those with hepatobiliary malignancies (100 % vs 37 %). It was concluded that the combined resection of the liver and pancreas can be performed safely. The need for combined partial hepatectomy and pancreatectomy to remove malignancy should not be considered a contraindication to resection in selected patients [592].

Although aggressive liver-directed therapy may be beneficial, liver-directed therapy may be associated with a high risk of complications after pancreaticoduodenectomy. Of 5025 patients who underwent pancreaticoduodenectomy at the Johns Hopkins Hospital and the Mayo Clinic between 1970 and 2008, 126 (2.5 %), patients were identified who were also treated with either simultaneous or staged liver-directed therapy. Data on demographics, primary tumor, and hepatic metastasis characteristics, as well as details of the liver-directed

therapy were collected and analyzed. Primary tumor histology included neuroendocrine carcinoma (35 %), pancreatic ductal adenocarcinoma (33 %), distal cholangiocarcinoma (9 %), ampullary carcinoma (7 %), duodenal carcinoma (4 %), or other (12 %). Liver-directed therapies included hepatic resection alone (45 %), hepatic resection plus ablation (11 %), ablation alone (8 %), transarterial chemoembolization (10 %), and whole-liver irradiation (22 %). The overall morbidity following liver-directed therapy was 34 percent and overall mortality was 2.4 percent. Patients undergoing staged liver-directed therapy (15 %) versus simultaneous pancreaticoduodenectomy plus liver-directed therapy (7 %) were significantly more likely to develop a liver abscess. Of those patients who developed complications, the majority (56 %) was major (Clavien grade ≥ 3). It was concluded that pancreaticoduodenectomy plus liver-directed therapy is associated with considerable morbidity. The incidence of hepatic abscess is increased in patients undergoing staged pancreaticoduodenectomy followed by liver-directed therapy [593].

There is limited information available about the feasibility and benefits of synchronous resection of liver metastases in patients with pancreatic and periampullary cancer undergoing pancreaticoduodenectomy. It was therefore reported on the experience with seven such patients. Analysis of the prospective database was carried out to identify patients who underwent synchronous resection of liver metastases with pancreaticoduodenectomy. Two-hundred and thirty patients underwent pancreaticoduodenectomy for pancreatic and periampullary cancer in the unit between 2003 and 2009. Seven patients (3 %) underwent synchronous resection of a solitary liver metastasis. In these patients, the operative time and intra-operative blood loss was marginally high as compared to the overall cohort of patients undergoing pancreaticoduodenectomy; however, the complication rates and the duration of the hospital stay were not affected. In patients undergoing resection of liver metastasis, there were 4 recurrences over a mean follow-up of 21 months. It was concluded that in patients with resectable pancreatic and periampullary cancer, the resection of a solitary liver metastasis can safely be performed together with a pancreaticoduodenectomy; however, its impact on improving survival has yet to be proven [594].

Laparoscopic pancreaticoduodenectomy

All 62 consecutive patients undergoing total laparoscopic pancreaticoduodenectomy from July 2007 through July 2009 at a single center were retrospectively studied regarding blood loss, operative time, postoperative morbidity, length of hospital stay, and 30-day or in-hospital mortality. The pancreaticojejunostomy consisted of a duct-to-mucosa anastomosis with interrupted suture. Median operative time was 368 minutes (range, 258-608 minutes) and median blood loss was 240 mL (range, 30-1200 mL). Diagnosis was pancreatic adenocarcinoma (n=31), intraductal papillary mucinous neoplasm (n=12), periampullary adenocarcinoma (n=8), neuroendocrine tumor (n=4), chronic pancreatitis (n=3), cholangiocarcinoma (n=1), metastatic renal cell carcinoma (n=1), cystadenoma (n=1), and duodenal adenoma (n=1). Median tumor size was 3 cm (range, 0.9-10.0 cm) and the median number of lymph nodes harvested was 15 (range, 6-31). Perioperative morbidity occurred in 26 patients and included pancreatic fistula (n=11), delayed gastric emptying (n=9), bleeding (n=5), and deep vein thrombosis (n=2). There was one postoperative mortality. Median length of hospital stay was 7 days (range, 4-69 days). It was concluded that laparoscopic pancreaticoduodenectomy is feasible, safe, and effective. Outcomes appear comparable with those via the open approach; however, controlled trials are needed [595].

Robotic surgery

Minimally invasive techniques and even robotics in pancreaticobiliary surgery are being used increasingly. Cost-effectiveness is a practical burden associated with the introduction of surgical innovation. One study compared the costs and the outcomes of open, laparoscopic, and robotic distal pancreatectomies. It was hypothesized that robotic distal pancreatectomy is cost-effective. Between 2008 and 2009, 77 distal pancreatectomies were performed at a single academic medical center. A retrospective analysis of prospectively collected data on demographics, short-term outcomes, and direct cost was performed. Thirty-two open distal pancreatectomies, 28 laparoscopic distal pancreatectomies, and 17 robotic distal pancreatectomies were performed. Age, American Society of Anesthesia preoperative risk score, and specimen length were similar. Indications for laparoscopic distal pancreatectomies and robotic distal pancreatectomies included more cystic neoplasms (49 %) and fewer malignancies (29 %) versus open distal pancreatectomies (16 % and 47 %). Spleen preservation occurred in 65 percent robotic distal pancreatectomies versus 12 percent and 29 percent in open distal pancreatectomies and laparoscopic distal pancreatectomies. The operative time averaged 298 minutes in robotic distal pancreatectomies versus 245 and 222 minutes in open distal pancreatectomies and laparoscopic distal pancreatectomies. Blood loss and morbidity were similar with no mortality. The length of stay was 4 days in robotic distal pancreatectomies versus 8 and 6 in open distal pancreatectomies and laparoscopic distal pancreatectomies. The total cost was USD 10,588 in robotic distal pancreatectomies versus USD 16,059 and USD 12,986 in open distal pancreatectomies and laparoscopic distal pancreatectomies. These data suggest direct hospital costs are comparable among all groups. They suggest a shorter length of stay in robotic versus laparoscopic or open approaches. Finally, spleen and vessel preservation rates may improve with a robotic approach at the expense of increased operative time [596].

Minimally invasive surgery is beneficial for complex operations; robotics may improve performance in these procedures; however, robotic pancreaticoduodenectomy has been plagued by long operative times. It was described a small series (n=5) of patients who underwent a hybrid pancreatoduodenectomy for treatment of obstructive jaundice and pancreatic mass. After diagnostic laparoscopy, the gallbladder was retracted cephalad and the porta hepatis was dissected. The lesser sac was opened to expose the superior mesenteric vein below the pancreas. Once the vein was cleared, the bile duct, stomach, pancreas, and jejunum were transected. After the uncinate process was cleared, the specimen was removed. The da Vinci S Surgical Robotic System was docked to perform a mucosa-to-mucosa pancreaticojejunostomy and an end-to-side choledochojejunostomy. A stapled gastrojejunostomy and drain placement completed the operation. Five patients underwent hybrid PD between pancreatoduodenectomy 2006 and 2007. All patients had a history of pancreatitis and presented with obstructive jaundice and a pancreatic mass. The operations were completed with 5 ports. The mean operative time was 7 hours. The mean hospital stay was 10 days. At 6 months after the operation, all patients were disease-free. It was concluded that complex procedures such as pancreatoduodenectomy can be accomplished with minimally invasive surgical techniques using robotic instrumentation [597].

Benign and borderline malignant pancreatic tumors are increasing. Function-preserving and minimally invasive pancreatectomy may be an ideal approach for these tumors. The authors retrospectively evaluated their initial experiences with five consecutive robotic central pancreatectomies (CPs). They also compared the perioperative outcome for open CPs performed in their institution. The five women in the study had a median age of 45 years (range 36-64 years). A solid pseudopapillary tumor of the pancreas was found in four patients, and a pancreatic endocrine tumor was found in one patient. The tumor was relatively small (median size, 1.5 cm; range, 1-2 cm). All remnant pancreases were managed using pancreaticogastrostomy. The median operation time was 480 min (range 360-480 min), and the median estimated intraoperative bleeding was 200 ml (range 100-600 ml).

No transfusion was given during the perioperative period. The median hospital stay was 12 days (range 9-28 days). Only one patient experienced postoperative pancreatic fistula (grade B), which was managed using the percutaneous drainage procedure. No operative mortality was noted. In a comparative analysis with open CP, the robotic CP group demonstrated a smaller asymptomatic tumor, a significantly longer operation time (287 ± 90 vs 432 ± 66 min), but less intraoperative bleeding. It was concluded that central pancreatectomy can be selected carefully as an appropriate surgical option for benign and borderline malignant lesions limited to the pancreatic neck area. The robotic surgical system may allow surgeons to perform complex and difficult laparoscopic procedures more easily, effectively, and precisely [598].

Robotic surgery is the most advanced development in minimally invasive surgery. However, the number of reports on robot-assisted endoscopic gastrointestinal surgery is still very small. In this article, we describe total laparoscopic pancreaticoduodenectomy (PD) undertaken using the da Vinci Surgical System®. Three patients underwent robotic PD 2009 - 2010. Following resection of the pancreatic head, duodenum, and the distal stomach, intracorporeal anastomosis was accomplished by Child's method of reconstruction, which includes a two-layered end-to-side pancreaticojejunostomy, an end-to-side choledochojejunostomy, and a side-to-side gastrojejunostomy. The time required for surgery was 703 ± 141 min, and blood loss was 118 ± 72 mL. The average hospital stay period was 26 ± 12 days. As a postoperative complication, pancreatic juice leak occurred in one case, but it was managed with conservative treatment. Of the three patients, one had cancer of the papilla of Vater, one had cancer of the pancreatic head, and one had a solid pseudopapillary neoplasm. In all cases, the surgical margin was negative for tumor. It was concluded that robot-assisted PD required a long time, but organ removal with less bleeding was able to be safely performed owing to the high degree of freedom associated with the forceps manipulation and the magnified view. Similarly, pancreatojejunostomy could certainly be conducted. No major postoperative complications were found [599].

Total pancreatectomy with islet transplantation

Total pancreatectomy (TP) with islet autotransplantation (IAT) to treat chronic pancreatitis (CP) was first performed at the University of Minnesota in 1977.¹ As of 2007, nearly 20 centers had performed TP-IAT with generally good outcomes in terms of pain relief and preservation of A-cell function. The addition of IAT to TP to maintain some insulin secretory capacity can prevent or minimize the otherwise inevitable postpancreatectomy diabetes mellitus, including in children. The ability to safely do a TP in a minimally invasive manner has potential to reduce morbidity and improve outcomes. In one report, it was described how it was done a robot-assisted laparoscopic TP and IAT for a patient with painful CP. After heparinization with 70 units/kg, the semipurified islets were infused into the portal vein via a small bowel venous tributary exposed through the Pfannenstiel incision. A total of 154,348 islets were injected; adjusted for size, 205,936 islet equivalents (IE) or 1974 IE/kg were embolized to the liver. Total operative time was approximately 15 hours with an estimated blood loss of 1200 mL. At 4 months after the surgery, he discontinued insulin and he has remained insulin independent and euglycemic ever since, now at 15 months postsurgery [600].

Image overlay surgery

It was applied a new concept of "image overlay surgery" consisting of the integration of virtual reality (VR) and augmented reality (AR) technology, in which dynamic 3D images were superimposed on the patient's actual body surface and evaluated as a reference for surgical navigation in gastrointestinal, hepatobiliary and pancreatic surgery. It was carried out

seven surgeries, including three cholecystectomies, two gastrectomies and two colectomies. A Macintosh and a DICOM workstation OsiriX were used in the operating room for image analysis. Raw data of the preoperative patient information obtained via MDCT were reconstructed to volume rendering and projected onto the patient's body surface during the surgeries. For accurate registration, OsiriX was first set to reproduce the patient body surface, and the positional coordinates of the umbilicus, left and right nipples, and the inguinal region were fixed as physiological markers on the body surface to reduce the positional error. The registration process was non-invasive and markerless, and was completed within 5 min. Image overlay navigation was helpful for 3D anatomical understanding of the surgical target in the gastrointestinal, hepatobiliary and pancreatic anatomies. The surgeon was able to minimize movement of the gaze and could utilize the image assistance without interfering with the forceps operation, reducing the gap from the VR. Unexpected organ injury could be avoided in all procedures. In biliary surgery, the projected virtual cholangiogram on the abdominal wall could advance safely with identification of the bile duct. For early gastric and colorectal cancer, the small tumors and blood vessels, which usually could not be found on the gastric serosa by laparoscopic view, were simultaneously detected on the body surface by carbon dioxide-enhanced MDCT. This provided accurate reconstructions of the tumor and involved lymph node, directly linked with optimization of the surgical procedures. The non-invasive markerless registration using physiological markers on the body surface reduced logistical efforts. The image overlay technique is a useful tool when highlighting hidden structures, giving more information [601].

NOTES

Natural orifice transluminal endoscopic surgery (NOTES) is a new concept that attempts to reduce the impact of surgery on the patient. In surgical oncology several studies have already revealed that a minimally invasive approach provides at least the same, if not a better, long-term outcome. One could hypothesize that a less invasive approach such as NOTES could further enhance such advantages. Since its initial description, NOTES has become clinical reality and today nearly every organ is accessible by a transluminal approach, in at least the experimental setting. Subsequent to published research, first clinical studies on NOTES in oncology were reported and the accuracy of transgastric peritoneoscopy for staging of pancreas cancer was shown to be similar to laparoscopy in humans. A NOTES gastro-jejunostomy via transgastric access has also been proposed to decrease invasiveness of palliative treatment of duodenal, biliary and pancreatic cancers. Colorectal cancer resection via transanal access would offer a clear-cut patient advantage over laparoscopic and would not be subject to the frequent criticism of violating an innocent second organ, as the colon or rectum is always breached in a colectomy. Natural orifice endoluminal therapies, such as endoscopic submucosal dissection, already have been clinically applied for several years. Improved techniques or instruments evolving from NOTES technology might enhance its widespread use for the treatment of early malignancies and thereby again will provide a tremendous benefit for the patient. Although still somewhat controversial, the subject of natural orifice surgery in oncological disease indicates that current laboratory efforts to introduce NOTES into cancer surgery could be ready for cautious clinical investigations. The final determination of patient benefit will need well-constructed prospective study [602].

Portal vein resection

The American Hepato-Pancreatico-Biliary Association and Society of Surgical Oncology published a consensus statement in 2009 on the subject of vein resection and reconstruction during pancreaticoduodenectomy (PD), and concluded that PD with vein resection and

reconstruction is a viable option for treatment of some pancreatic adenocarcinomas. Now one article described the current approaches and recent advances in the management, staging, and surgical techniques regarding portal vein resection. With proper patient selection, a detailed understanding of the anatomy of the root of mesentery, and adequate surgeon experience, vascular resection and reconstruction can be performed safely and does not impact survival duration. Isolated venous involvement is not a contraindication to PD when performed by experienced surgeons at high-volume centers as part of a multidisciplinary and multimodal approach to localized pancreatic cancer [603].

A systematic review objectively evaluated the safety and outcomes of extended pancreaticoduodenectomy with vascular resection for pancreatic cancer involving critical adjacent vessels namely the superior mesenteric-portal veins, hepatic artery, superior mesenteric artery, and celiac axis. Electronic searches were performed on two databases from January 1995 to August 2009. The end points were: firstly, to evaluate the safety through reporting the mortality rate and associated complications and, secondly, the outcome by reporting the survival after surgery. This was synthesized through a narrative review with full tabulation of results of all included studies. Twenty-eight retrospective studies comprising of 1,458 patients were reviewed. Vein thrombosis and arterial involvement were reported as contraindications to surgery in 62 percent and 71 percent of studies, respectively. The median mortality rate was 4 percent (range, 0 % to 17 %). The median R0 and R1 rates were 75 percent (range, 14 % to 100 %) and 25 percent (range, 0 % to 86 %), respectively. In high volume centers, the median survival was 15 months (range, 9 to 23 months). Nine of 10 (90 %) studies comparing the survival after extended pancreaticoduodenectomy with vascular resection versus standard pancreaticoduodenectomy reported statistically similar survival outcomes. Undertaking vascular resection was not associated with a poorer survival. It was concluded that the morbidity, mortality, and survival outcome after undertaking extended pancreaticoduodenectomy with vascular resection for pancreatic cancer with venous involvement and/or limited arterial involvement is acceptable in the setting of an expert referral center and should not be a contraindication to a curative surgery [604].

Polytetrafluoroethylene (PTFE) graft

Use of prosthetic grafts for reconstruction after portal vein (PV) resection during pancreaticoduodenectomy is controversial. It was examined outcomes in patients who underwent vein reconstruction using polytetrafluoroethylene (PTFE). A review of prospectively maintained databases at three centers identified all patients who underwent pancreaticoduodenectomy (PD) with vein resection and reconstruction using PTFE grafts between 1994 and 2009. Patient, operative, and outcomes variables were studied. Graft patency and survival were assessed using the Kaplan-Meier technique. Thirty-three patients underwent segmental vein resection with interposition PTFE graft reconstruction. Median age was 67 years; median Eastern Cooperative Oncology Group score was 1. Most operations were performed for pancreatic adenocarcinoma (85 %); 96 percent were T3 lesions or greater. Standard PD was performed in 12 (36 %) patients, pylorus-preservation in 17 (52 %), and total pancreatectomy in 4 (12 %). Combined resection of portal and superior mesenteric veins (SMV) was required in 49 percent, with resection isolated to PV in 12 percent and SMV in 39 percent. Splenic vein ligation was necessary in 30 percent. Median graft diameter was 12 mm (range 8 to 20 mm), with the majority being ring-enforced (73 %). Median operative and vascular clamp times were 463 and 41 minutes, respectively, with median blood loss of 1,500 mL. The negative margin rate was 64 percent. Overall morbidity rate was 46 percent, and 30-day mortality was 6 percent. No patients developed irreversible hepatic necrosis or graft infection. Pancreatic fistulas occurred in 3 (9 %). With mean follow-up of 14 months, overall graft patency was 76 percent. Estimated median duration of graft patency was 21 months. Median survival was 12 months for pancreatic adenocarcinoma. It was concluded that with careful patient selection, PTFE graft reconstruction of resected PV/SMV during pancreaticoduodenectomy is possible with minimal risk of hepatic necrosis or

graft infection. Comparison studies to primary anastomosis and autologous vein reconstruction have not been done [605].

Balloon enteroscopy of the pancreatic duct after pancreaticoduodenectomy

Balloon enteroscopy is a new procedure that allows deep access to the small bowel and has been used to access the biliary system in patients with surgically altered anatomy. It was described the successful use of single-balloon enteroscopy to access the pancreatic duct after pancreaticoduodenectomy. A 67-year-old man was referred for the management of recurrent episodes of acute pancreatitis in 2007, after a Whipple procedure for pancreatic adenocarcinoma in 1999. Magnetic resonance imaging revealed an atrophic pancreas and a dilated pancreatic duct. No pancreatic masses were seen. Endoscopic retrograde cholangiopancreatography with a duodenoscope and a pediatric colonoscope was attempted. Because of postoperative changes in the stomach and marked looping of the endoscopes, the pancreaticojejunostomy could not be accessed. Therefore, a single-balloon enteroscope was used to access the pancreaticojejunostomy through the gastrojejunostomy. After advancement of the single-balloon overtube into the gastroenterostomy, the balloon was inflated and the enteroscope was advanced into the afferent limb until the pancreaticojejunostomy was seen. The orifice was stenosed to a small pinhole 1 to 2 mm in diameter. Contrast injection revealed an irregular and dilated main pancreatic duct. The opening was dilated to 4 mm using a balloon. A 5F pancreatic stent was placed in the pancreatic duct. Six weeks later, a second dilation was performed with a 6-mm dilating balloon with good effect. After the procedure, the patient remained free of pain and attacks of acute pancreatitis [606].

Tumors of the body and tail

Solid lesions of the body and tail of the pancreas challenge all the diagnostic and technical skills of the modern gastrointestinal surgeon. The information available from modern computed tomography (CT), magnetic resonance (MR), and endoscopic ultrasound (EUS) imaging provide diagnostic and anatomic data that give the surgeon precise information with which to plan an operation and to discuss with the patient during the preoperative visit. A preoperative evaluation includes a thorough history and a pancreas protocol CT scan, supplemented by MR imaging and EUS when needed, to differentiate between the various potential diagnoses. These same modalities can be essential in proper staging in the case of malignant lesions, thus aiding in management decisions. Most lesions ultimately require operative resection, barring metastatic disease, with the notable exception of autoimmune pancreatitis [607].

It was evaluated prognostic indicators for distal pancreatectomy with regional lymph node dissection in pancreatic body or tail carcinoma. Between 1993 and 2008, 50 patients with ductal carcinoma of the body or tail of the pancreas who underwent distal pancreatectomy with regional lymph node dissection were retrospectively analyzed. Clinicopathological factors associated with patient survival were evaluated. No in-hospital deaths occurred among the study patients. The overall 5-year survival rate was 19 percent, and median survival was 23 months. Univariate analysis revealed that lymph node metastasis, intrapancreatic neural infiltration, peripancreatic nerve plexus infiltration, and tumor differentiation affected patient survival significantly. Multivariate analysis validated lymph node metastasis as an independent prognostic factor. Moreover, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and the number of metastasis in the lymph nodes attached to the pancreas was significantly associated with survival after surgical resection. Lymph node metastasis was a significant and independent prognostic

factor for the surgically resected pancreatic body or tail carcinoma. Furthermore, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and these lymph nodes were potential indicators predicting both tumor extension and survival after surgery for pancreatic body or tail carcinoma [608].

Post-surgical prognosis

The post-resection outcomes and factors influencing post-resection survival for adenocarcinoma of the body and tail of the pancreas were analyzed to determine the effectiveness of surgery. A total of 73 patients with adenocarcinoma of the body or tail of the pancreas who underwent resection between 1994 and June 2007 were evaluated for overall survival. Multiple malignancies were present in 34 of 73 patients (47 %). Overall 1-, 3- and 5-year survival rates after surgery were 79 percent, 34 percent, and 30 percent, respectively. Presence of symptoms, multiple cancers and level of preoperative tumor marker did not influence post-resection survival. As for tumor characteristics, tumor size, histological tumor differentiation, retroperitoneal invasion, status of residual tumor and UICC staging represented significant prognostic indicators by univariate analysis. Gemcitabine, when administered as an adjuvant setting, strongly worked for improving post-resection outcome (5-year survival rate 51 %). Factors shown to have independent prognostic significance on multivariate analysis were tumor size (<3 vs \geq 3 cm), status of residual tumor (R0 vs R1, 2), and postoperative administration of gemcitabine. This means that appropriate patient selection and accurate surgical technique with postoperative adjuvant therapy could benefit survival of patients with carcinoma of the pancreas body and tail [609].

Laparoscopic left-sided pancreatectomy

Laparoscopic resection is regarded as safe and feasible in selected patients with benign pancreatic tumours. Few data exist on laparoscopic surgery for malignant lesions and larger neoplasms in unselected patients. One study included all patients admitted to a university hospital 1997-2009 for surgery of lesions in the body and tail of the pancreas, and selected patients with lesions in the pancreatic head, who underwent surgery by a laparoscopic approach with curative intent. A total of 166 patients had 170 operations, including 138 pancreatic resections, 18 explorations, nine resections of peripancreatic tissue and five other therapeutic procedures. Four patients had repeat procedures. There were 53 endocrine tumours (31 %), 28 pancreatic carcinomas (16 %), five cases of metastases (3 %), 48 cystic tumours (28 %) and 37 other lesions (22 %). The total morbidity rate was 17 percent. Fistula was the most common complication (10 %). Three patients needed reoperation for complications. There were three hospital deaths (2 %). Median hospital stay following surgery was 4 days. It was concluded that laparoscopic resection of lesions in the body and tail of the pancreas in an unselected patient series was safe and feasible, and should be the method of choice for this patient group in specialized centres [610].

A review was done of all distal pancreatectomies performed between 2003 and 2009 at Memorial Sloan-Kettering Cancer Center. Variables were compared between laparoscopic and open groups in unmatched and matched analyses. During the 7-year study period, 343 distal pancreatectomies were performed; 107 (31 %) were attempted laparoscopically and 236 (69 %) were performed open. The conversion rate was 30 percent. Laparoscopic patients were significantly younger (median 60 vs 64 years), experienced less blood loss (median 150 vs 350 mL), longer operative times (median 163 vs 194 minutes), shorter hospital stay (median 5 vs 7 days), and had fewer postoperative complications (27 % vs 40 %) than open patients. The rates of complications of grade 3 or greater (20 % vs 20 %) and pancreatic leak (15 % vs 13 %) were similar between laparoscopic and open groups. Patients having procedures that were converted had a higher body mass index (BMI) than patients who did not (28 vs 25). Patients with converted resections experienced higher rates

of complications of grade 3 or greater (36 % vs 20 %) and pancreatic leaks (27 % vs 13 %) than open patients. Compared with matched open patients, laparoscopic patients had longer operative times (195 minutes vs 160 minutes), less blood loss (175 mL vs 300 mL), and shorter hospital stay (5 days vs 6 days). It was concluded that patients who had laparoscopic distal pancreatectomy experienced decreased blood loss and a shorter hospital stay compared with matched patients undergoing open resection. Careful patient selection is important because patients who required conversion experienced higher rates of complications and pancreatic leak [611].

As compared with open distal pancreatectomy (ODP), laparoscopic distal pancreatectomy (LDP) affords improved perioperative outcomes. Records from patients undergoing distal pancreatectomy (DP) for PDAC from 2000 to 2008 from 9 academic medical centers were reviewed. Short-term (node harvest and margin status) and long-term (survival) cancer outcomes were assessed. A 3:1 matched analysis was performed for ODP and LDP cases using age, American Society of Anesthesiologists (ASA) class, and tumor size. There were 212 patients who underwent DP for PDAC; 23 (11 %) of these were approached laparoscopically. For all 212 patients, 56 (26 %) had positive margins. The mean number of nodes examined was 12.6 ± 8.4 and 114 patients (54 %) had at least 1 positive node. Median overall survival was 16 months. In the matched analysis there were no significant differences in positive margin rates, number of nodes examined, number of patients with at least 1 positive node, or overall survival. Logistic regression for all 212 patients demonstrated that advanced age, larger tumors, positive margins, and node positive disease were independently associated with worse survival; however, method of resection (ODP vs LDP) was not. Hospital stay was 2 days shorter in the matched comparison, which approached significance (LDP, 7 days vs ODP, 9 days) It was concluded that LDP provides similar short- and long-term oncologic outcomes as compared with OD, with potentially shorter hospital stay. These results suggest that LDP is an acceptable approach for resection of PDAC of the left pancreas in selected patients [612].

Precise and expedient localization of small pancreatic tumors during laparoscopic distal pancreatectomy can be difficult owing to the decreased tactile ability of laparoscopy and the homogenous appearance of the surrounding retroperitoneal fat. Precise localization of the lesion is critical to achieving adequate margins of resection while preserving as much healthy pancreas as possible. The objective in one study was to determine the effect of endoscopic tattooing of the distal pancreas on operative time. It was reviewed retrospectively 36 consecutive patients who had a laparoscopic distal pancreatectomy at our institution over a 4-year period (2006-2009). Ten patients underwent preoperative tattooing via an endoscopic transgastric technique using ultrasound guidance. The tattoo was performed using 2-4 cc of sterile purified carbon particles injected immediately proximal and anterior to the pancreatic lesion. Operative times were compared according to the presence of a tattoo. The endoscopically placed tattoo was easily visible upon entering the lesser sac in all 10 patients at laparoscopy. Patients with a tattoo had a significantly shorter operative time (median, 129 minutes; range, 53-180) compared with patients without a tattoo (median, 180 minutes; range, 120-240). None of the tattoo group required repeat surgery, whereas 1 patient who was not tattooed required re-resection for a lesion missed in the initial specimen. There were no complications associated with the endoscopic ultrasound-guided tattoo. It was concluded that endoscopic ultrasound-guided tattooing of pancreas lesions before a laparoscopic distal pancreatectomy is safe and is associated with decreased operative time compared with nontattooed patients. This technique can allow for quick and precise localization of the lesion, allowing for optimal preservation of pancreas parenchyma and demarcating an appropriate line of resection [613].

Techniques in distal pancreatectomy

Suture closure and stapler closure of the pancreatic remnant after distal pancreatectomy are the techniques used most often. The ideal choice remains a matter of debate. Five

bibliographic databases covering 1970 to July 2009 were searched. Sixteen articles met the inclusion criteria. Stapler closure was performed in 671 patients, while suture closure was conducted in 1,615 patients. The pancreatic fistula rate ranged from 0 percent to 40 percent for stapler closure of the pancreatic stump and from 9 percent to 46 percent for the suture closure technique. There were no significant difference between the stapler and suture closure groups with respect to the pancreatic fistula formation rate (22 % vs 31 %; odds ratio, 0.85; 95 % confidence interval 0.66 to 1.08), although there was a trend toward favoring stapler closure. In 4 studies including 437 patients, stapler closure was associated with a trend (not statistically significant) toward a reduction in intra-abdominal abscess (odds ratio, 0.53; 95 % confidence interval 0.24 to 1.15). It was concluded that no significant differences occur between suture and stapler closure with respect to the pancreatic fistula or intra-abdominal abscess after distal pancreatectomy, though there is a trend favoring stapler closure [614].

With gastric resection

The use of laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer (EGC) and laparoscopic distal pancreatectomy (LDP) for lesions of benign or borderline malignancy have gained worldwide acceptance because they are viewed as safe and feasible. A 59-year-old man was diagnosed with EGC and intraductal papillary mucinous neoplasm (IPMN) simultaneously during cancer screening. LDP was performed prior to LADG due to the possibility of splenectomy. After completing LDP, LADG was performed in the usual manner. LADG combined with spleen-preserving LDP was performed safely. The operating time was 561 minutes, and there was no intraoperative complication. The patient was discharged on postoperative 10 without any complications. No recurrence or distant metastasis occurred during the subsequent 40 months. LADG combined with spleen-preserving LDP for EGC and IPMN was found to be feasible and less invasive than open surgery [615].

Distal pancreatectomy with celiac axis resection

Traditionally, vascular invasion by a pancreatic tumor negated the possibility of surgery, but developments in vascular resection technique have expanded the pool of patients who are candidates for surgery. In 1953, Appleby described distal pancreatectomy and total gastrectomy with en bloc resection of the celiac axis as a treatment of locally advanced gastric cancer. After celiac axis resection, adequate blood flow to the foregut is maintained by collateral circulation between the superior mesenteric artery (SMA) and the hepatobiliary system via an intact pancreaticoduodenal arcade. En bloc celiac axis resection, with a number of modifications, has since been used to treat locally advanced cancer of the pancreatic body. It was now presented a case of a patient underwent distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic adenocarcinoma after gemcitabine-based neoadjuvant chemotherapy and radiation. Biopsy of pericealic tissue was negative for tumor on frozen section, indicating that an en bloc celiac axis resection could potentially yield negative vascular margins. The patient was successfully extubated on postoperative day 1 and experienced no further respiratory or metabolic complications. The patient's postoperative course was otherwise uneventful aside from watery diarrhea controlled by loperamide, pancrealipase, and empiric therapy for *Clostridium difficile* colitis with metronidazole. Surgical pathology revealed a 2.5 cm poorly differentiated ductal adenocarcinoma of the pancreatic body. However, most of the mass was composed of dense fibrous tissue with only minimal viable tumor cells in a cluster of less than 0.2 cm; this finding was surmised to be a result of the neoadjuvant chemotherapy. Surgical margins were clear, and 12 peripancreatic and 3 perisplenic lymph nodes were free of tumor. One year after surgery, the patient is doing well. Her most recent imaging showed no signs of recurrent disease, and her CA19-9 has remained within the reference range. However, she continues to experience chronic diarrhea, despite maximal pancrealipase supplementation and antidiarrheal agents, and has difficulty maintaining weight [616].

Body-tail pancreatic cancer is an aggressive disease with a low resectability rate and a poor prognosis. Celiac axis invasion usually contraindicates resection. The aim of one study was to analyze the feasibility of distal pancreatectomy (DP) with celiac axis resection (DP-CAR) for locally advanced body-tail pancreatic cancer. All DPs performed between 1989 and 2007 were considered. DP and DP-CAR were reviewed for pre-, intra- and postoperative data. An extensive, detailed literature review on DP and DP-CAR was also performed. DP was performed in 49 of our patients, and 745 cases were retrieved from the literature. The overall morbidity and mortality rates were 32 percent and 3.0 percent, respectively. It was performed DP-CAR in five patients with no mortality but 80 percent morbidity. A further 90 patients were retrieved from the literature. Arterial reconstruction was needed in 1/5 of our patients and in 13/90 of patients in the literature. Collaterals from superior mesenteric artery maintained adequate hepatic artery blood flow in the remaining 81 patients. The overall morbidity and mortality rates were 41 percent and 2.1 percent, respectively. The median survival ranged between 5 and 25 months after DP and was 13 months after DP-CAR [617].

Surgery in elderly

Surgery offers the only chance for cure in patients with pancreatic cancer, and a growing number of elderly patients are being offered resection. It was examined outcomes after pancreaticoduodenectomy in patients 80 years and older. It was retrospectively collected data on pancreaticoduodenectomy patients from 1992 to 2009 to compare outcomes between patients older and younger than 80 years. Patients 80 years and older who underwent pancreaticoduodenectomy were similar with respect to gender, race, blood loss, operative times, reoperation, length of stay, and readmission compared to younger patients. There were no differences in overall complications (47 % vs 51 %), major complications (19 % vs 25 %), and mortality (5 % vs 4 %) when comparing older to younger patients. In a subset who underwent pancreaticoduodenectomy for ductal adenocarcinoma, older patients (n=45) had a median survival time of 12 months compared to 18 months in younger patients (n=346). It was concluded that pancreaticoduodenectomy can be performed safely in select patients 80 years and older. Age alone should not dissuade surgeons from offering patients resection, though elderly patients with pancreatic ductal adenocarcinoma appear to have shorter survival than younger patients with the same disease [618].

It was reviewed morbidity and mortality in patients aged 65 years and older undergoing curative intent surgery in two centers in the Czech Republic. Data were retrieved by retrospective analysis of the medical records over the period 2000-2007. In total, 60 patients were included. The mean age was 71 years (median 70 years; range 65-85 years). Most patients (43, 72 %) underwent hemipancreatoduodenectomy, combined in 4 with portomesenteric vessel resection. Twelve patients (20 %) had distal pancreatectomy and 5 patients (8%) total pancreatectomy. Overall morbidity was 28 percent. Only 10 patients (18 %) developed serious surgical complications in terms of pancreatic leak (5, 8 %), biliary leak (2, 3 %), and intra-abdominal inflammatory collection (4, 7 %). Four patients (7 %) died within 30 days. The 1-year survival was 63 percent. It was concluded that age per se is not a contraindication to surgery. Patient's overall general condition, co-existing co-morbidities, and ability to get over with any potential complications are more important [619].

Surgical results overall

Recently, hospital and surgeon volume is widely discussed as a prognostic factor after major pancreatic surgery. It was now presented the experience regarding major pancreatectomy in a middle-volume center. During the last 11 years, 66 patients underwent major

pancreatectomy (pancreaticoduodenectomy, n=52; distal pancreatectomy with splenectomy, n=13; and central pancreatectomy, n=1). Postoperative course and long-term outcome were recorded and analyzed. One patient died after pancreaticoduodenectomy for ampullary cancer (total mortality of approximately 1.5 % for the whole group of patients or 1.9 % for the group of patients who underwent pancreaticoduodenectomy). None of the patients was reoperated on. Transient pancreatic fistula was observed in 46 patients (36 patients after pancreaticoduodenectomy, 69, and 10 patients after distal pancreatectomy, 77 %). Two patients required percutaneous computed tomography-guided drainage of fluid collections, whereas in another one, a tube thoracostomy was performed to drain a pleuritic fluid collection. Delayed gastric emptying was observed in 6 patients after pancreaticoduodenectomy. Median survival for the whole group of patients was 17 months. The authors concluded that major pancreatic resections can be performed safely, with acceptable morbidity and mortality and good long-term results, even in middle-volume centers. However, experience is required from the part of the operating surgeon [620].

Impact of preoperative diabetes mellitus

Associations between diabetes mellitus (DM) and pancreatic ductal adenocarcinoma (PDAC) are well established; however, the impact of DM on perioperative morbidity and mortality after PDAC resection is unclear. A prospectively maintained database review identified all patients undergoing PDAC resection between 2000 and 2008. Diagnosis of DM was established by history and biochemical profile. Records were reviewed for comorbidities, operative variables, and histologic parameters. Postoperative morbidity and mortality were assessed for diabetic and nondiabetic patients using standardized definitions. Of 251 PDAC cases, 116 (46 %) patients had preoperative DM. Pancreaticoduodenectomy was performed in 220 (88 %), left pancreatectomy in 29 (12 %), and total pancreatectomy in 2 (1 %). The major complication rate was 26 percent, with 60-day mortality of 4 percent. Delayed gastric emptying (DGE) occurred in 40 percent of patients. Pancreatic fistulas developed in 17 (7 %) patients; 11 of them were clinically significant (grades B/C). DM patients had a significantly higher likelihood of developing fistulas (DM 10 %, non-DM 4 %). When controlled for age, comorbidities, body mass index, preoperative albumin level, operation type, operative time, and pancreatic quality, DM maintained an independent association with fistula formation (odds ratio 4.3; 95 % confidence interval 1.18 to 15.8). Acute kidney injury was more frequent in the DM group (DM 23 %, non-DM 13 %). DM and non-DM patients had similar frequency of DGE, wound infections, intra-abdominal abscesses, and cardiovascular and pulmonary complications, as well as length of stay and mortality. It was concluded that comorbid diabetes mellitus does not influence perioperative outcomes dramatically after pancreatectomy for ductal adenocarcinoma. The role of pancreatic cancer-associated diabetes mellitus as a risk factor for postresection pancreatic fistula should be further explored. Evaluation of glycemic control and outcomes after PDAC resection may be useful [621].

Complications, overview

Many definitions are used in the literature for pancreatic anastomotic failure (PAF) and delayed gastric emptying (DGE) after pancreaticoduodenectomy (PD). To promote homogeneity, published reports after 2005 have used the International Study Group on Pancreatic Surgery (ISGPS) consensus definition for PAF and DGE; however, subsequent authors have had to interpret or modify the ISGPS classification to make it useable. The solution might be to create a web-based calculator, test it for ambiguity and reliability with a large number of cases, and then make it available to the public. Using 507 consecutive patients undergoing PD and 14 questions, it was created a web-based calculator based on the ISGPS classification to assess the incidence and grade of clinical impact (none,

moderate, or major deviation) for PAF and DGE. As the calculator's formulas were tested, ambiguous terms were identified and resolved. The incidence for cases with clinical impact from PAF was 10 percent and from DGE it was 12 percent. Multivariate analysis identified 4 factors predictive for PAF: male sex, body mass index (BMI) >30 kg/m², soft gland texture, and main pancreatic duct size ≤3 mm. Predictive factors for DGE included 2 factors: not using a surgical microscope, and simultaneous PAF. It was summarized that a web-based calculator had been developed to promote homogeneity of method for grading of PAF and DGE after PD. Anyone with access to the web can now compare their results to the current study [622].

Postoperative MRSA-infection

One study evaluated the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) hospital-acquired infection on postoperative complications and patient outcome after pancreatoduodenectomy (PD). Seventy-nine patients who underwent PD were monitored for hospital-acquired MRSA. The patients were grouped as (1) no MRSA infection, (2) skin colonization with MRSA, and (3) systemic MRSA infection. Results: Forty (51%) of the 79 patients were MRSA positive during hospital admission. Fourteen of the 40 patients swabbed for MRSA were found positive (skin colonization), and 26 patients (33%) developed systemic MRSA infection after PD. The sites of MRSA infection included (1) abdominal drain fluid (16/26; 42 %), (2) sputum (4/26; 15 %), (3) blood cultures (2/26; 8 %), and (4) combination of sites (9/26; 35 %). The patients with systemic MRSA infection had a longer postoperative stay (31 vs 22 days) and increased incidence of chest infections compared with MRSA-negative patients (14 vs 4). Four of the 16 patients with MRSA-positive drain fluid had a postpancreatectomy hemorrhage compared with 3 of the 63 patients with no MRSA infection in drain fluid. It was concluded that of the 79 patients admitted for PD, 51 percent became colonized with MRSA infection. Systemic hospital-acquired MRSA infection in 33 percent was associated with prolonged postoperative stay, increased wound and chest infections, and increased risk of postoperative hemorrhage [623].

Postoperative delayed gastric emptying (DGE)

Delayed gastric emptying (DGE) is one of main complications after pylorus-preserving pancreaticoduodenectomy (PPPD) with regional lymph node dissection (RLND). The aim of one study was to retrospectively investigate whether subtotal stomach-preserving PD (SSPPD) decreased incidence of DGE. The study included 112 consecutive patients underwent PPPD (n=48) or SSPPD (n=64) with/without RLND. DGE was classified into three categories (grades A, B, and C) according to the guideline proposed by the International Study Group of Pancreatic Surgery. The incidence of DGE grade B/C in SSPPD with RLND (13 %) was significantly lower compared with that (34 %) in PPPD with RLND. Consequently, the mean length of postoperative hospital stay of SSPPD with RLND group was significantly shorter than that of PPPD with RLND. It was concluded that SSPPD could be substituted for PPPD due to decreased postoperative DGE when RLND is involved [624].

Delayed gastric emptying (DGE) is a common complication after pancreatoduodenectomy. The International Study Group of Pancreatic Surgery (ISGPS) definition of DGE has not been evaluated and validated in a high-volume centre. It was evaluated complete data sets including assessment of gastric emptying were identified from a database of patients undergoing pancreatoduodenectomy between 2001 and 2008. Factors associated with DGE (grades A, B and C) were assessed by univariable and multivariable analyses. DGE occurred in 340 (45 %) of 764 patients. Median hospital stay was significantly prolonged in patients with DGE: 13, 21 and 40 days for grades A, B and C respectively versus 11 days for patients

without DGE. DGE was associated with prolonged intensive care unit (ICU) admission (at least 2 days): 21, 29, and 62 percent of those with grades A, B and C respectively versus 9 percent of patients without DGE. Factors independently influencing DGE grade A were female sex, preoperative heart failure and major complications (grade III-V). Validation of the DGE definition revealed that DGE grades A and B were associated with interventional treatment in 20 and 44 percent of patients. It was concluded that the ISGPS DGE definition is feasible and applicable in patients with an uneventful postoperative course. Major postoperative complications and ICU treatment, however, might limit its usefulness. The identified risk factors for DGE are not amenable to perioperative improvement [625].

Postoperative pancreatic fistula

Evaluating the ISGPF criteria

Pancreatic fistula (PF) after pancreatoduodenectomy (PD) remains a challenging problem. Now 100 consecutive patients underwent PD. All data, including commonly accepted risk factors for PF and PF defined according to the International Study Group of Pancreatic Fistula, were collected prospectively. On the pancreatic margin, a score of fibrosis and a score of fatty infiltration were assessed by a pathologist blinded to the postoperative course. PF occurred in 31 percent of patients. In univariate analysis, male sex, age greater than 58 years, body mass index (BMI) ≥ 25 , pre-operative high blood pressure, operation for nonintraductal papillary and mucinous neoplasm (IPMN) disease and for ampullary carcinoma, operative time, blood loss, soft consistency of the pancreatic remnant, absence of pancreatic fibrosis, and presence of fatty infiltration of the pancreas were associated with a greater risk of PF. In a multivariate analysis, only BMI ≥ 25 , absence of pancreatic fibrosis, and presence of fatty pancreas were significant predictors of PF. A score based on the number of risk factors present divided the patient population into 4 subgroups carrying a risk of PF that ranged from 7 percent (no risk factor) to 78 percent (3 risk factors) and from 0 percent to 81 percent, taking into account only symptomatic PF (grade B and C). It was concluded that the presence of an increased BMI, the presence of fatty pancreas, and the absence of pancreatic fibrosis as risk factors of PF allows a more precise and objective prediction of PF than the consistency of pancreatic remnant alone. A predictive score based on these 3 factors could help to tailor preventive measures [626].

Risk factors

The purpose of one study was to determine whether patients who develop a pancreatic fistula after pancreatoduodenectomy are more likely to have higher pancreatic fat levels than matched controls and if so, to investigate whether preoperative dual gradient-echo magnetic resonance (MR) imaging can be used to measure pancreatic fat and predict the development of postoperative pancreatic fistula. Pancreatic fistula is a major complication and its most frequently reported risk factors tend to be anatomic features of the pancreatic remnant, such as a soft pancreatic texture. Between 2007 and 2007, a total of 96 cases of pancreatoduodenectomy were performed. Of total, 20 patients (21 %) who developed a pancreatic fistula were carefully matched for multiple parameters including age, gender, pancreatic pathology, surgeon, and type of operation with 20 control patients who did not develop a pancreatic fistula. In the pancreatic fistula group, 9 patients (45 %) had a grade A fistula and 11 (55 %) grade B fistula. Degrees of pancreatic fatty infiltration and fibrosis were assessed quantitatively. In-phase and opposed-phase images were obtained by dual-gradient-echo MR imaging. Percentage decreases in pancreatic signal intensity on opposed-phase images relative to those on in-phase images were calculated and defined as relative signal intensity decreases (RSID). More patients in the pancreatic fistula group had a soft pancreatic texture or a smaller pancreatic duct and total fat and RSID were significantly higher. In soft

pancreatic texture group, intralobular, interlobular, and total fat were significantly elevated. Furthermore, pancreatic fat levels were found to be significantly correlated positively with RSID. RSID was correlated with total pancreatic fat and when an RSID criterion more than 7.032 was used, pancreatic fistula could be predicted as 73 percent sensitivity and 76 percent specificity. The findings suggest that increased pancreatic fat is a risk factor of postoperative pancreatic fistula. Preoperative measurements of pancreatic fat by MRI offer a noninvasive predicting the occurrence of pancreatic fistula [627].

After proximal pancreatectomy: value of drain data

Post-operative pancreatic fistula (POPF) is a common and potentially devastating complication of pancreas resection. The aim of one study was to evaluate whether drain data accurately predicts clinically significant POPF. A prospectively maintained database with daily drain amylase concentrations and output volumes from 177 consecutive pancreatic resections was analysed. Drain data, demographic and operative data were correlated with POPF (ISGPF Grade: A - clinically silent, B - clinically evident, C - severe) to determine predictive factors. Twenty-six (46 %) out of 56 patients who underwent distal pancreatectomy and 52 (43 %) out of 121 patients who underwent a Whipple procedure developed a POPF (Grade A-C). POPFs were classified as A (24, 43 %) and C (2, 4 %) after distal pancreatectomy whereas they were graded as A (35, 29 %), B (15, 12 %) and C (2, 2 %) after Whipple procedures. Drain data analysis was limited to Whipple procedures because only two patients developed a clinically significant leak after distal pancreatectomy. The daily total drain output did not differ between patients with a clinical leak (Grades B/C) and patients without a clinical leak (no leak and Grade A) on post-operative day (POD) 1 to 7. Although the median amylase concentration was significantly higher in patients with a clinical leak on POD 1-6, there was no day that amylase concentration predicted a clinical leak better than simply classifying all patients as "no leak" (maximum accuracy 86 % on POD 1, expected accuracy by chance 86 percent). It was concluded that drain amylase data in the early post-operative period are not a sensitive or specific predictor of which patients will develop clinically significant POPF after pancreas resection [628].

After distal pancreatectomy

Pancreatic fistulae post distal pancreatectomy still leads to significant morbidity and if not properly managed, may lead to mortality. The identification of risk factors and effective management of patients with pancreatic fistulae is important in the prevention of these complications. There were 75 open consecutive distal pancreatectomies in one department of surgery from 2001 to 2007. The indications for operation were neuroendocrine tumours (n=15), adenocarcinoma (n=20), intraductal papillary mucinous tumour (IPMT) (n=20), serous cysts (n=15) and trauma (n=5). There were 20 patients (27 %) who developed pancreatic fistulae in the whole series. On univariate analysis, the patients with pancreatic fistulae had significantly more pre-morbidities, softer pancreas and use of staplers as a method of closure of the pancreatic remnant. On multivariate analysis, the use of staplers and soft pancreas were significant independent risk factors for the development of pancreatic fistulae in our patient population. All of the patients with pancreatic fistulae were successfully treated non-surgically with no mortality in the whole series. It was concluded that the use of stapler on soft pancreas leads to a higher risk for pancreatic fistulae after distal pancreatectomies. Most pancreatic fistulae can be managed non-surgically with good outcome [629].

Resection of the body and tail of the pancreas (distal pancreatectomy) is associated with high postoperative morbidity, most of which is due to leakage from the pancreatic transection surface. The aim of one study was to analyze factors which may affect the risk of pancreatic fistula formation. All consecutive distal pancreatectomies prospectively registered in one hospital database from 1999 to 2007 were included. Clinically relevant pancreatic fistula

grades B and C, defined according to the International Study Group on Pancreatic Fistula (ISGPF) definition were assessed. The impact of patient, tumor, surgery, and radiology-related factors on the risk of pancreatic fistula formation were assessed by univariate and multivariate analyses. A distal pancreatectomy was performed in 51 patients (median age: 59 years; range: 26-76 years), 22 of whom had malignant and 29 benign or premalignant disease. Pancreatic fistulas were diagnosed in 17 (33 %) of the patients. An additional three patients had a local abscess without apparent but assumed pancreatic leakage. Multivariate analysis showed that pancreatic fistulas occurred significantly more frequently after hand suturing of the transection area versus the use of a stapler (69 % vs 21 %; OR 40.4, 95 % confidence interval 3.4 to 486) and a large volume of the pancreatic remnant (greater, or equal to, 34 cm³) increased the subsequent risk of pancreatic fistula (57 % vs 21 %; OR 6.14, 95 % confidence interval 1.14 to 39.0). It was concluded that the volume of the remaining pancreas and the technique of closure of the transected pancreas were found to affect this risk, thus allowing future preventive measures to be explored and evaluated in clinical trials [630].

Delayed arterial bleeding

Delayed hemorrhage after pancreaticoduodenectomy is a rare but lethal complication, for which angiography has become an essential diagnostic and therapeutic tool. Because of their location, the hepatic artery and the gastroduodenal artery stump are particularly exposed to erosion by bile and pancreatic juice in cases of anastomotic leaks. Bleeding from these vessels require hemostatic maneuvers that spare arterial hepatic flow. Delayed hemorrhage after pancreatoduodenectomy results from erosion or pseudoaneurysm of major visceral arteries secondary to anastomotic leaks and local sepsis. Because of their anatomic location near pancreatic and biliary anastomosis, the hepatic artery and the gastroduodenal artery stump are the first victims of bile and pancreatic juice. Bleeding from these vessels requires hemostatic maneuvers that spare arterial hepatic flow. Indeed, hepatic artery occlusion carries theoretical risks of (1) bile duct ischemia leading to intrahepatic bilioma, biliary anastomotic leaks, and/or secondary stenosis; and (2) hepatic infarction with subsequent intrahepatic abscess formation and the risk of hepatocellular failure. Therefore, various hemostatic measures have been recommended to preserve arterial hepatic blood flow, such as covered stent insertion. Nevertheless, endovascular stenting sometimes proves impossible because of the anatomy of the common artery. Moreover, studies have not assessed the efficiency of covered stents (only case reports exist), and stent insertion introduces the risk of prosthetic infection and further hemorrhage due to the required drugs for platelet aggregation inhibition. Nevertheless, when anatomical factors prevent these maneuvers, hepatic artery embolization may be essential to achieve hemostasis, but this may theoretically harm both the liver and the biliary tract, as described after liver transplantation. It was reported four cases of hepatic artery occlusion for delayed hemorrhage after pancreatoduodenectomy. Between 2007 and 2008, it was performed 77 pancreaticoduodenectomies. From this sample, four patients presented with delayed hemorrhage that required hepatic artery embolization. Two patients presented bile duct carcinoma, 1 had pancreatic adenocarcinoma, and the fourth had intraductal papillary mucinous neoplasm of the main pancreatic duct. Lymphadenectomy including removal of all neural and lymph nodes of the hepatic artery and the right side of the superior mesenteric artery was always performed. Pancreatic anastomosis was performed with the stomach in two patients and with the jejunum in two others. All patients presented with abdominal complications before hemorrhage: 3 with pancreatic fistula diagnosed by a drain output of an amylase-rich fluid and one with biliary anastomotic insufficiency. Hemorrhage occurred at 18th, 20th, 24th, and 72nd postoperative days. Clinical signs of bleeding were hematemesis associated with hemodynamic shock for two patients and sentinel bleeding (defined as discrete blood loss via abdominal drains with spontaneous cessation of hemorrhage) in the

two others. After resuscitation maintaining hemodynamic stability, an abdominal contrasted computed tomography was performed. Three patients bled from the gastroduodenal artery stump and one from the common hepatic artery. It was performed angiographic embolization in all patients. Three patients had pseudoaneurysms whose anatomy necessitated complete hepatic artery embolization. The fourth patient underwent selective embolization of the gastroduodenal artery stump, which was long enough, during the resection of intraductal papillary mucinous neoplasm; because of rebleeding at the fourth day after embolization, hemostasis was achieved with complete common hepatic artery embolization. All had intact portal venous perfusion. After complete embolization, no one rebled. All patients displayed minor and temporary disturbances in hepatic function, but any patient presented liver failure defined as association of jaundice and encephalopathy. Hepatic abscesses developed in two patients; those were limited to two segments (left lobe for one patient and segments VI and VII for the other) and responded successfully to antibiotic therapy and percutaneous drainage, although this resulted in longer hospital stays (60 and 74 days vs 34 and 15 days). All patients survived 1 year after surgery. Surgical approaches to delayed hemorrhage after pancreatoduodenectomy seem an efficient strategy in surgical series, with hemostatic success rates equivalent to embolization. However, relaparotomy presents two principal inconveniences: (1) the anatomic inaccessibility of the vessels behind the anastomotic reconstruction often necessitates the reversal of the biliary and pancreatic anastomoses; and (2) dissection is hazardous because of adhesions and inflammation, which increase with postoperative delay. Moreover, control of hepatic artery bleeding often needs its ligation because its reconstruction is rarely possible owing to very fragile walls. Surgery can combine treating the etiology of the hemorrhage with pancreatectomy completion or surgical drainage to prevent further erosion by pancreatic fistula and local sepsis [631].

Peroperative known portal vein embolism

In advanced pancreatic cancer with portal tract infiltration, there is no effective systemic therapy, and only extended pancreatectomy with portal vein resection, aimed at obtaining cancer-free surgical margins, enables an improved prognosis. Portal venous tumor embolism is a serious form of the vascular invasion in hepatocellular carcinoma and other malignant tumors. In pancreatic tumors, there have been some reports of portal venous tumor embolism caused by intraductal papillary-mucinous carcinoma and malignant islet cell tumor. However, portal venous embolism in pancreatic ductal adenocarcinoma has never been reported. It was now presented two rare resected cases of pancreatic ductal adenocarcinoma with extensive portal venous tumor embolism. It was a 58-year-old woman who was hospitalized because of upper abdominal pain and white faeces. She was diagnosed with obstructive jaundice due to advanced pancreatic head cancer with portal invasion and underwent endoscopic retrograde biliary drainage. Tumor marker values were as follows: carcinoembryonic antigen, 1.9 ng/mL (<5.0 ng/mL); carbohydrate-associated antigen 19-9, 1002 U/mL (<37 U/mL). Abdominal enhanced multidetector computed tomography showed a poorly enhanced mass of 40-mm diameter in the head of the pancreas, infiltrating the superior mesenteric vein (SMV). Moreover, derived from the site of invasion, CT imaging of the portal phase revealed an extensive defect from the SMV to the main trunk of the portal vein. It was diagnosed portal venous tumor embolism based on these findings. On positron-emission tomography (PET)-CT imaging, accumulation of fluorodeoxyglucose (FDG) was seen in the main tumor, but not in the site of portal vein occlusion. Because systemic evaluation did not reveal a distant metastasis, we performed pancreaticoduodenectomy with portal vein resection including tumor embolism and intraoperative radiation therapy (30 Gy). Portal vein reconstruction was done with end-to-end anastomosis between the SMV and the main trunk of the portal vein. Postoperative histopathologic examination revealed moderately differentiated tubular adenocarcinoma with portal vein tumor embolism invading the vascular endothelium and lymph node metastases

on the anteroinferior surface of the pancreas and around the middle colic vein. Case 2 was a 75-year-old woman who was diagnosed with a pancreatic tumor by abdominal ultrasound on a regularly scheduled check-up. Upon closer inspection, she was diagnosed with advanced pancreatic body cancer with portal invasion. Tumor marker values were as follows: carcinoembryonic antigen, 1.9 ng/mL (<5.0 ng/mL); carbohydrate-associated antigen 19-9, 20 U/mL (<37 U/mL). Abdominal enhanced multidetector CT revealed a poorly enhancing mass of 25-mm diameter in the body of the pancreas that directly invaded the splenic vein. Moreover, there was an extensive defect from the splenic vein to the hepatic portal region leading up from the site of invasion, as well as marked collateral veins toward the liver. On PET-CT imaging, accumulation of FDG was seen in the main tumor, but not in the site of portal vein occlusion. Because there was no distant metastasis found on a systemic workup, it was performed distal pancreatectomy with portal vein resection including tumor embolism and intraoperative radiation therapy (30 Gy). It was not reconstruct the portal vein because collateral vessels were preserved intact. Postoperative histopathologic diagnosis confirmed moderately differentiated tubular adenocarcinoma with portal vein tumor embolism invading the vascular endothelium. There was no lymph node metastasis. Because pancreatoduodenectomy with portal vein resection can improve the prognosis of patients with pancreatic cancer infiltrating the portal vein, it was performed an aggressively method using an anti-thrombotic catheter (Anthrion bypass catheter). The major reason for the lack of reported resection of pancreatic ductal adenocarcinoma with extensive portal venous tumor embolism is its high histological malignancy grade. Concurrent with intraportal progression, pancreatic cancer frequently invades the nerve plexi, lymph nodes, and major arteries such as the common hepatic artery and the superior mesenteric artery. Moreover, it ultimately results in inoperable tumors because of liver metastasis or peritoneal dissemination. At present, there is no explicit consensus on the treatment of pancreatic cancer with extensive portal venous tumor embolism. However, it was proposed that pancreatic resection should be considered in cases of possible cancer-free surgical margins as well as those with portal vein. Portal venous tumor embolism develops in pancreatic ductal adenocarcinoma after the tumor cells initially enter the PV via direct invasion and subsequently extend while infiltrating the vascular endothelium. In hepatocellular carcinoma, the tumor embolism can be removed with comparative ease at the time of surgery because typically it is soft and grows expansively once the tumor cells enter the portal vein. In contrast, it is necessary to remove the entire invaded portal vein together with the tumor in pancreatic cancer because of vascular endothelial infiltration [632].

Postoperative portal vein thrombosis

To assess patients with chronic portal vein thrombosis (PVT) with respect to transcapsular collateral veins, the communication between these veins and ectopic varices, and the cause of PVT 145 consecutive patients 2003-2008 with chronic PVT due to a variety of causes were assessed for transcapsular collaterals and ectopic varices with ultrasonography (US). Transcapsular collaterals were detected in 15 (10 %) of 145 patients with chronic PVT. They were restricted to patients with a history of hepatobiliary surgery, severe pancreatitis, or abdominal surgery (n=21) and were not detected in patients with liver cirrhosis, systemic coagulopathy, extrahepatic malignancy, idiopathic PVT, chronic pancreatitis, or infectious or inflammatory diseases (n=124). Ectopic varices were infrequent in 70 patients with liver cirrhosis (n=2, 3 %) but were significantly common in 14 patients with PVT after hepatobiliary surgery (n=9, 64 %) (odds ratio 21.4). Direct communication between transcapsular collaterals and ectopic varices was visible in all nine patients in this cohort. In eight of these patients, ectopic varices were found to be the bleeding source in gastrointestinal hemorrhage. It was concluded that transcapsular collaterals frequently occur in patients with chronic PVT due to hepatobiliary surgery or necrotizing pancreatitis. They are associated with

ectopic varices; therefore, awareness of transcapsular collaterals in this patient subgroup will help to localize ectopic varices as potential bleeding source [633].

Postoperative thrombotic occlusion of the portal vein is one of the most serious complications after pancreatectomy with portal vein resection. If the condition advances rapidly to complete occlusion, the patient will lapse into a critical condition of intestinal necrosis from intense congestion because pancreatic cancer surgery with extensive lymph node dissection requires ligation of the splenic vein. There has been no report of the frequency of thrombotic complete occlusion of the portal vein after pancreatectomy with portal vein resection. The main cause of portal vein thrombus is surgical technique. Both the retained thrombus formed while clamping the portal vein system for anastomosis and the disturbed blood flow caused by stenosis or hypertonicity of the anastomosis site can produce a portal vein thrombus. Therefore, cautious anastomotic procedure and thorough washing out of the portal vein are needed. Abdominal Doppler ultrasound and enhanced CT scans are of value in diagnosing portal vein thrombus. Doppler ultrasound is especially useful for assessing temporal change because of its convenience and noninvasiveness. Generally, systemic anticoagulation is administered for portal vein thrombus patients without severe obstructive signs of the portal vein system, such as bowel wall edema. However, for severe occlusion, thrombectomy should be performed immediately as a second surgery. Now it was reported two rare cases of thrombotic occlusion of the portal vein immediately after pancreatectomy with portal vein resection. The patients survived by thrombectomy in a second surgery. Case 1 was of a 67-year-old woman who underwent total pancreatectomy with portal vein and spleen resections for pancreatic cancer with portal invasion. The operation time and the hemorrhage volume of the initial surgery were 441 minutes and 1900 mL, respectively. Although it was made an end-to-end anastomosis between the portal vein and the superior mesenteric vein (SMV) using an antithrombogenic catheter for a portocaval catheter bypass, an anastomotic stricture was seen in the first attempt. Therefore, it was anastomosed again during the first operation. Soon after the first operation, a large volume of thin bloody drainage developed through an intraperitoneal tube, and a state of shock was seen. The patient exhibited a poor response to large amounts of fluid replacement, blood transfusion, and catecholamine. A day after surgery, it was detected the disappearance of intrahepatic portal vein blood flow by Doppler ultrasound. Moreover, an abdominal enhanced computed tomographic scan showed disruption of the portal vein due to extended thrombus, edematous swelling of the small intestine, and excess ascites fluid. Then, it was performed a second operation for thrombotic occlusion of the portal vein 24 hours after the first operation. Intraoperatively, there was abundant hemorrhagic ascites. The entire small intestine showed dark-red heat, severe congestion, and edematous change. It was reconstructed the portal vein using a left external iliac venous graft after opening the anastomosis site to remove the thrombus. Then, it was implanted a small catheter in the portal vein from the branch of the SMV that was used for the portocaval bypass. From the time reconstruction was completed, the color and the edema of the small intestine improved remarkably. After the second surgery, vital signs stabilized. At 28 postoperative days, it was confirmed the patency of the portal vein by abdominal enhanced CT scan. Eventually, the patient was discharged 63 days after the second surgery. Case 2 was of a 51-year-old man who underwent pancreaticoduodenectomy with portal vein resection for pancreatic cancer that involved portal. The operation time and the hemorrhage volume of the initial surgery were 570 minutes and 912 mL, respectively. It was ligated the splenic vein at the section merging with the SMV. An end-to-end anastomosis was made between the portal vein and the SMV using an antithrombogenic catheter for portocaval bypass. Because thrombosis was observed near the anastomosis site intraoperatively, the thrombus was removed, and we anastomosed again and placed the small catheter in a branch of the SMV to the portal vein. Although his general condition was good postoperatively, a large volume of serous fluid continued through a drainage tube. The day after surgery, it was detected restricted intrahepatic portal vein blood flow by Doppler ultrasound. Portal angiography was performed from the catheter, and thrombotic occlusion of the portal vein was diagnosed. Then, a second operation was performed 22 hours after the

first operation. Intraoperatively, the ascites fluid appeared serous, and congestion of the small intestine was mild. It was reconstructed the portal vein directly after opening the anastomosis site to remove the thrombus. After the second surgery, the discharge from the drainage tube decreased. At 14 postoperative days, it was confirmed the patency of the portal vein by abdominal enhanced CT scan. The patient was discharged 31 days after the second surgery [634].

Postoperative diabetes

Hyperproinsulinaemia has been reported in patients with type 2 diabetes. It is unclear whether this is due to an intrinsic defect in beta-cell function or secondary to the increased demand on the beta-cells. It was investigated whether hyperproinsulinaemia is also present in patients with secondary diabetes, and whether proinsulin levels are associated with impaired β -cell area or function. Thirty-three patients with and without diabetes secondary to pancreatic diseases were studied prior to pancreatic surgery. Intact and total proinsulin levels were compared with the pancreatic beta-cell area and measures of insulin secretion and action. Fasting concentrations of total and intact proinsulin were similar in patients with normal, impaired (including two cases of impaired fasting glucose) and diabetic glucose tolerance. There were no differences in the total proinsulin/insulin or intact proinsulin/insulin ratio between the groups. There was a weak inverse association between the total proinsulin/insulin ratio and pancreatic beta-cell area, whereas the intact proinsulin/insulin ratio and the intact and total proinsulin levels were unrelated to beta-cell area. However, a strong inverse relationship between homeostasis model assessment index of beta-cell function and both the total and the intact proinsulin/insulin ratio was found. The association of insulin resistance with intact proinsulin was much weaker than the correlation with fasting insulin. It was concluded that hyperproinsulinemia is associated with defects in insulin secretion rather than a reduction in beta-cell area. The weak association between intact proinsulin and insulin resistance argues against the usefulness of this parameter in clinical practice [635].

Postoperative renal function

In a study of estimated glomerular filtration rate compared to measured creatinine clearance for predicting postoperative renal dysfunction in patients undergoing pancreatoduodenectomy the records of 139 patients were enrolled, and preoperative creatinine clearance, a 3-variable equation for eGFR (eGFR3) and a 5-variable equation for eGFR (eGFR5) were estimated. The maximum increases in the postoperative serum creatinine and urea nitrogen levels were compared between the groups with normal and abnormal levels relative to creatinine clearance, eGFR3, and eGFR5. There were 30 patients with abnormal clearance levels, 17 with abnormal eGFR3 levels, and 16 with abnormal eGFR5 levels. Postoperative serum creatinine and urea nitrogen levels were significantly higher in patients with eGFR3 and eGFR5 abnormal levels than in patients with eGFR3 and eGFR5 normal levels. Postoperative serum creatinine and urea nitrogen levels tended to be higher in patients with abnormal clearance level. The sensitivity and specificity of eGFR3 and eGFR5 for postoperative renal dysfunction were better than those of creatine clearance, and multivariate analysis showed that eGFR5 was the only independent predictive factor for postoperative renal dysfunction. The eGFR5 and eGFR3, rather than the creatine clearance, are recommended as preoperative renal function test in patients undergoing pancreatoduodenectomy [636].

Sequelae after pancreatoduodenectomy

Relatively little is known about the gastrointestinal function after recovery of a pancreatoduodenectomy. One review focused on the functional changes of the stomach, duodenum and pancreas that occur after pancreatoduodenectomy. Although the mortality in relation to pancreatoduodenectomy has decreased over the years, it remains associated with considerable morbidity, which occurs in 40-60 percent of patients. Physical complaints early after the operation are often caused by motility disorders, in particular delayed gastric emptying, which occurs in up to 40 percent of patients. During longer follow-up of these patients the occurrence of endocrine and exocrine pancreatic insufficiency becomes more predominant. The main presenting symptoms of exocrine insufficiency are weight loss and steatorrhea. Its presence is suspected on clinical ground and can be supported by fecal elastase-1 measurement. Exocrine insufficiency can be compensated with oral enteric-coated enzyme supplements. The quality of life issue will be addressed as an important outcome measurement after pancreaticoduodenectomy [637].

Remote metastases

Metastatic tumors within the cervix are uncommon if one excludes endometrial carcinoma, which involves the cervix by direct spread. A variety of other neoplasms rarely metastasize to the cervix and, in most cases, the diagnosis is straightforward because of a combination of clinical and pathologic parameters, common features of metastatic carcinoma within the cervix including predominant involvement of the deep stroma, absence of surface involvement and of an in situ component, and prominent lymphovascular permeation. It was describe 6 cases of metastatic adenocarcinoma involving the cervix with superficial "mucosal" involvement mimicking primary cervical adenocarcinoma or adenocarcinoma in situ. In 5 cases, the primary adenocarcinoma was in the ovary or peritoneum and was of serous (4 cases) or clear-cell (1 case) type. In the other case, the primary neoplasm was in the pancreas and this was initially interpreted as a primary cervical adenocarcinoma. It is important for the pathologist to be aware of the possibility of cervical mucosal metastasis to avoid an erroneous diagnosis of a primary cervical adenocarcinoma or adenocarcinoma in situ [638].

Abdominal wall metastasis

A 74-year-old woman underwent laparotomy for pancreatic cancer, which revealed peritoneal dissemination. Then, gastrojejunostomy was performed. After the operation, multiple liver metastases were detected by CT scanning. However, there were no findings suggestive of peritoneal dissemination. The patient was treated with chemotherapy of gemcitabine plus S-1. At the end of five courses, the primary lesion and liver metastases decreased in size. Nevertheless, a painful hard tumor was noticed at the scar of the previous operation in the upper abdomen. Biopsy examination revealed adenocarcinoma. Accordingly, abdominal wall metastasis from pancreatic cancer was diagnosed. It was speculated that the abdominal wall metastasis grew by implantation into the scar because good control of the primary lesion and liver metastasis was maintained. Metastasis to the abdominal wall has been rarely reported. Moreover, the available literature contains only two reports on such metastasis from pancreatic cancer [639].

Palliation

Prophylactic gastrojejunostomy

To determine whether prophylactic gastrojejunostomy should be performed routinely in patients with unresectable periampullary cancer. It was searched the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, issue 3), MEDLINE, EMBASE and Science Citation Index Expanded until April 2010. It was included randomised controlled trials comparing prophylactic gastrojejunostomy versus no gastrojejunostomy in patients with unresectable periampullary cancer (irrespective of language or publication status): Two authors independently assessed trials for inclusion and independently extracted data. It was analysed data with both the fixed-effect and the random-effects models using Review Manager. It was calculated the hazard ratio (HR), risk ratio (RR), or mean difference (MD) with 95% confidence intervals (CI) based on an intention-to-treat or available case analysis. It was identified two trials (of high risk of bias) involving 152 patients randomised to gastrojejunostomy (80 patients) and no gastrojejunostomy (72 patients). In both trials, patients were found to be unresectable during exploratory laparotomy. Most of the patients also underwent biliary-enteric drainage. There was no evidence of difference in the overall survival (HR 1.02; 95 % confidence interval 0.84 to 1.25), peri-operative mortality or morbidity, quality of life, or hospital stay (mean difference 0.97 days) between the two groups. The proportion of patients who developed long term gastric outlet obstruction was significantly lower in the prophylactic gastrojejunostomy group (2/80; 3 %) compared with no gastrojejunostomy group (20/72; 28 %) (RR 0.10; 95 % confidence interval 0.03 to 0.37). The operating time was significantly longer in the gastrojejunostomy group compared with no gastrojejunostomy group (MD 45 minutes). The authors concluded that routine prophylactic gastrojejunostomy is indicated in patients with unresectable periampullary cancer undergoing exploratory laparotomy (with or without hepaticojejunostomy) [640].

Duodenal stent

Gastroduodenal obstruction due to malignancy can be difficult to palliate. Self-expanding metal stents (SEMS) are gaining acceptance as an effective alternative to surgical bypass. Patients not suitable for surgical bypass, with complete gastric outlet obstruction as a result of malignancy, were offered palliation with SEMS from 2004 to 2008. The procedure was performed under fluoroscopic guidance and conscious sedation. Data were collected prospectively. Seventy patients underwent SEMS placement (hepatobiliary and pancreatic malignancy, 44; antral gastric carcinoma, 19; other, 7). Follow-up was complete in 69 patients (99 %). Technical and clinical success rates were 93 and 95 percent, respectively. Median hospital stay was 2 (range 1-18) days, median survival was 1.8 (0-19) months, and 87 percent had improved intake after SEMS placement, as determined by Gastric Outlet Obstruction Severity Score before and after stenting. Complications included two episodes of minor bleeding. The use of SEMS to alleviate complete malignant gastric outlet obstruction in patients with limited life expectancy is successful in re-establishing enteral intake in most patients, with minimal morbidity, no mortality and a short hospital stay [641].

Biliary stent

It was prospectively evaluated the usefulness of MDCT using a curved planar reformation technique for the noninvasive assessment of the causes of biliary stent occlusion in patients with malignant biliary obstruction. Between 2004 and 2009, 173 patients with unresectable malignant biliary obstruction underwent biliary stent insertion. Among them, 26 patients with suspected biliary stent occlusion underwent 29 sessions of ERCP within 2 weeks after MDCT was performed. Curved planar reformation images were obtained along the pathway

of the biliary stent. It was interpreted tissue growth or stent clogging by comparing attenuation values inside the biliary stent between the unenhanced and contrast-enhanced phases of CT. The cause of biliary stent occlusion was confirmed by using ERCP. The differences in attenuation value inside the biliary stent between the contrast-enhanced and unenhanced phases of CT in the tissue growth group was 28 ± 22 HU and 4 ± 11 HU in the stent-clogging group, a significant difference. The sensitivity and specificity of MDCT for the diagnosis of tissue growth were 87 percent and 86 percent, respectively. The overall accuracy of curved planar reformation images of MDCT for diagnosing the causes of stent occlusion was 86 percent. It was concluded that curved planar reformation MDCT is a useful noninvasive technique that is relatively accurate for diagnosing the cause of biliary stent occlusion and is helpful for planning the therapeutic management of such patients [642].

Laparoscopic cholecystojejunostomy

Optimization of quality of life is an important goal in the management of patients with unresectable peri-ampullary cancer. It was reported two cases to demonstrate the feasibility of scarless transumbilical single-incision laparoscopic cholecystojejunostomy using conventional instruments in the management of unresectable peri-ampullary cancer. Two 58-year-old patients (one male) underwent transumbilical single-incision laparoscopic cholecystojejunostomies: The male and female patients were diagnosed with duodenal papillary carcinoma and pancreatic cancer, respectively. The hepatocystic junction was confirmed patent preoperatively in both patients. A 2-cm periumbilical incision was made for the placement of three trocars. Conventional rigid laparoscopic instruments were solely used throughout the procedure, and operative techniques were carried out in the same fashion as for conventional laparoscopic cholecystojejunostomy. The procedures were completed uneventfully in 190 and 155 min, respectively, with no complications, and the blood loss was estimated at 80 and 20 mL, respectively. Postoperative pain scores on postoperative day 1 were 4/10 and 3/10. The patients were discharged from the hospital on postoperative days 3 and 5 with resolving jaundice. It was concluded that transumbilical single-incision laparoscopic cholecystojejunostomy appears to be a technically feasible alternative to standard laparoscopic procedure and can be performed using conventional laparoscopic instruments [643].

Pancreatic cancer during pregnancy

Acute, persistent abdominal pain due to ruptured pancreatic carcinoma and perforated stomach is extremely rare during pregnancy. It was evaluated a woman at 34 weeks of gestation presenting with uterine contractions. Computed tomography scanning revealed a large retroperitoneal mass, and her blood carbohydrate antigen 19-9 level was elevated. Immediately after an emergency cesarean delivery, pancreatic cancer was detected, and pancreatoduodenectomy was performed. The patient underwent chemotherapy and remains disease-free at 2 years. Delayed diagnosis and treatment are associated with high morbidity of both neonate and mother in cases of pancreatic cancer during pregnancy. Computed tomography scanning and carbohydrate antigen 19-9 levels are useful for diagnosis, after which radical surgery should be performed immediately in late pregnancy [644].

Risk of suicide

Depression is highly prevalent in patients with pancreatic cancer and can result in fatal outcomes from suicides. The authors report suicide rates among patients with pancreatic cancer in the United States and identify factors associated with greater suicide rates. The study reviewed data in the SEER database for patients diagnosed with pancreatic

adenocarcinoma from 1995 to 2005. Logistic regression models were used to perform multivariate modeling for factors associated with suicide, while Kaplan-Meier analysis was used to assess factors affecting survival. Among 36,221 patients followed for 22,145 person-years, the suicide rate was 135 per 100,000 person-years. The corresponding rate in the US population aged 65-74 years was 13 per 100,000 person-years, with a standardized mortality ratio (SMR) of 10.8 (95 % confidence interval 9.2 to 12.7). Significantly greater suicide rates were noted in males (odds ratio 13.5; 95 % confidence interval 3.2 to 56.9) and, among males, in patients undergoing an operative intervention (OR 2.5; 95 % confidence interval 1.0 to 6.5). Married men had a lesser risk of committing suicide (OR 0.3 95 % confidence interval 0.1 to 0.6). Median survival among patients undergoing operative intervention was 2 months for those who committed suicide compared with 10 months for those who did not commit suicide. It was concluded that male patients with pancreatic adenocarcinoma have a risk of suicide nearly 11 times that of the general population. Patients who undergo an operative intervention are more likely to commit suicide, generally in the early postoperative period [645].

Experimental

Animal models

In the last 10 years, there has been a relative explosion of new rodent systems that recapitulate both genetic and cellular lesions that lead to the development of pancreatic cancer. These models now need to be considered when selecting an appropriate in vivo system to study disease etiology, cell signaling, and drug development. The majority of these evaluations have used transplantation of cancer cells and the use of carcinogens, which still maintain their value when investigating human cancer and epigenetic contributors. Xenograft models utilize cultured or primary pancreatic cancer cells that are placed under the skin or implanted within the pancreas of immunocompromised mice. Carcinogen-induced systems rely on administration of certain chemicals to generate cellular changes that rapidly lead to pancreatic cancer. Genetically modified mice are more advanced in their design in that relevant genetic mutations can be inserted into mouse genomic DNA in both a conditional and inducible manner. Generation of mice that develop spontaneous pancreatic cancer from a targeted genetic mutation is a valuable research tool, considering the broad spectrum of genes and cell targets that can be used, producing a variety of neoplastic lesions and cancer that can reflect many aspects of human pancreatic ductal adenocarcinoma [646].

Cryosurgery

To test the feasibility of cryosurgery for pancreatic carcinoma and to observe the consequence of cryosurgery by 2 different techniques 12 healthy pigs underwent laparotomy, during which, chop amputation of common bile duct and duodenum were performed, meanwhile other intra-abdominal organs with the pancreas were isolated. Two different techniques of cryosurgery were performed on the pancreas. Group A (n=6) accepted the mild hypothermic cryosurgery with liquid nitrogen superficial refrigeration, and group B (n=6) were performed with the deep hypothermic cryosurgery at -170 °C with LCS2000 cryogenic surgical system. All the animals' digestive tract was reconstructed with cholecystojejunostomy and gastroenterostomy, respectively. Acute necrotizing pancreatitis occurred on all animals in group A, of which 5 of the 6 died within 1 week, whereas only 1 of the 6 reported a 4-week survival. All animals in group B survived during the observation, in which only a transient increment and a gradual correction of pancreatic amylase level were recorded. Small pancreatic pseudocyst occurred in 1 case. Thus, mild hypothermic cryosurgery with liquid nitrogen superficial refrigeration might lead to pancreatic injury and induce acute pancreatitis, whereas deep hypothermic cryosurgery with adequate time

showed a promising effect in destroying pancreatic tissue and preventing acute pancreatitis [647].

Pain treatment

In inoperable malignancy, pain relief with opioids is often inadequate. Nerve block procedures may improve symptom control. The aim of one study was to assess celiac plexus block (CPB) and thoracoscopic splanchnicectomy (TS) in patients receiving appropriate medical management. Patients with confirmed irresectable malignancy of the pancreas or upper abdominal viscera who required opioid analgesia were randomized to medical management alone, medical management + CPB, or medical management +TS. Randomization was stratified by treatment centre, tumour type and previous opioid medication. The primary endpoint was pain relief at 2 months. Sixty-five patients (58 pancreas cancer) were randomized, 18 withdrew or died within 2 months. Effective pain relief was achieved in only one third of subjects at 2 weeks, and just under half at 2 months (medical management: 6/19 and 5/12 evaluable patients; CPB: 5/14 and 5/9; TS 4/14 and 4/11). There were no significant differences between the groups in pain scores or opioid consumption, and there was no correlation between continued use of opioids and effective pain relief. Previous randomized studies have shown small differences in pain scores, but no difference in opioid consumption and quality of life. The absence of any benefit from interventions in the present study questions their value [648].

Case reports

Variceal bleeding

Variceal bleeding outside the esophagus and stomach is rare but important because of its difficult diagnosis and treatment. Bleeding from cholecystojejunostomy varices has been reported to be a late complication of palliative biliary surgery for chronic pancreatitis. Such ectopic variceal bleeding has never been reported after palliative surgery for pancreatic cancer, probably because of the limited lifespan of these patients. It was reported a successful experience using endoscopic cyanoacrylate sclerotherapy to treat bleeding from cholecystojejunostomy varices in a 57-year-old man with pancreatic head cancer [649].

Pancreatitis or pancreatic cancer?

Pancreatitis and pancreatic carcinoma are the most common diseases of the pancreas, which may occur independently or be the cause and the effect, respectively. Pancreatitis with atypical imaging presentations is often maldiagnosed as pancreatic carcinoma. In patients with coexistence of pancreatic carcinoma and pancreatitis, the pathologic condition of pancreatic carcinoma is often exaggerated, leading to inappropriate selection of a therapeutic regimen. In one article, it was presented a case of pancreatitis maldiagnosed as pancreatic carcinoma. The CT and the MRI examination results 21 days after an acute onset showed that there was an irregular, space-occupying lesion in the pancreatic head on the abdominal side, with insufficient blood supply, low T1WI signal, and high T2WI signal, and there was formation of emboli in the superior mesenteric-portal vein, which was diagnosed as carcinoma of the pancreatic head accompanied with formation of cancer embolism in the superior mesenteric-portal vein. Seven months after the diagnosis of pancreatic carcinoma, the patient underwent MRI reexamination, and it was found that there was residual fat deposition in the pancreatic head and that the superior mesenteric-portal vein became patent and thinner. The carbohydrate antigen 19-9 (CA19-9) level of the patient had been normal since the onset of the disease. The final diagnosis was acute onset of chronic pancreatitis

accompanied with formation of thrombosis in the superior mesenteric-portal vein. Pancreatitis is different from pancreatic carcinoma mainly in cancer embolism in the splenic and superior mesenteric-portal veins and capsulation of the splenic artery and abdominal aorta by parapancreatic emboli. Vascular invasion in pancreatitis is mainly represented by formation of embolism of local or adjacent vessels. This case of pancreatitis-complicated pathological change of the splenic and the superior mesenteric-portal veins was maldiagnosed as vascular invasion. A careful examination would tell that the thrombotic vein is not thickened and not enhanced on the enhancement scan. A follow-up several months later would probably show that the thrombotic vein may be obstructed or reopened [650].

PANCREATIC CANCER, CHEMOTHERAPY ± RADIOTHERAPY

Overviews

In the last decade the approach to drug development in pancreatic cancer has included a focus on combinations of cytotoxic agents. While some promising results were seen in phase II studies, none of the phase III trials of cytotoxic combinations were able to demonstrate an improvement in overall survival over that seen with the single-agent gemcitabine. Newer studies have assessed the efficacy of “targeted” agents that inhibit pathways thought to be important in the development, growth, invasion and metastasis of pancreatic cancer. Although some agents had promising activity in preclinical studies, none has made a major impact in the clinic. There has been some success with the addition of the EGF receptor tyrosine kinase inhibitor erlotinib to gemcitabine, which was the first combination to achieve an overall survival benefit compared with gemcitabine alone in a phase III trial. Future directions for drug development in pancreatic cancer will mainly involve testing new targeted agents, although some cytotoxic combinations are currently in phase III testing. There is a need to better understand the biology of the disease and incorporate this into trials in an attempt to search for predictive and prognostic markers that will aid in drug development. Control of pancreatic cancer will require combinations of targeted agents, probably individualized based on tumor genetics [651].

Surgery remains the only treatment for pancreatic cancer offering an advantage in terms of overall survival (5-year survival range, 15-25 percent), but unfortunately only 10-20 percent of patients present resectable disease at the time of diagnosis. Hence chemotherapy, possibly combined with radiation therapy, remains the only treatment option aimed at palliation of symptoms and ensuring a better quality of life. Notwithstanding the efforts to find more effective therapies for the treatment of pancreatic cancer, significant results have not yet been achieved. Increasing interest has focused on integrated treatments, i.e. chemotherapy combined with targeted therapies, and a better selection of patients. One study examines the principal clinical trials that will help give clinicians an overview of the progress made in the systemic therapy for advanced pancreatic cancer patients in recent years [652].

Afflicting approximately 37,000 Americans yearly with pancreatic cancer, more than 80 percent of patients are unresectable and, therefore, incurable at the time of their diagnosis. Although surgical resection offers the only opportunity for cure, it remains largely unsuccessful; most patients who are candidates for surgical resection relapse and die in fewer than 5 years. This mortality leaves a 5-year overall survival of about 4 percent for patients diagnosed with pancreatic cancer. Perhaps the most daunting realization for physicians involved in the management of this disease is the understanding that these numbers have not changed in more than 30 years. As surgery remains the foundation of curative therapy for pancreatic cancer, it is time to review the data on adjuvant chemotherapy and adjuvant chemotherapy with radiotherapy as efforts to boost cure rates [653].

About 7,200 new cases of pancreatic adenocarcinoma are diagnosed each year in France. At the time of diagnosis, only 20 percent of patients have an operable tumor; 30 percent have local or regional extensions and 50 percent metastatic dissemination. Median survival of patients after surgical resection ranges from 12 to 20 months, because of the high relapse rate. Currently, the use of radiotherapy is controversial for patients with operable or locally advanced pancreatic cancer. The standard treatment is six months of chemotherapy with FUFOL or gemcitabine. Combining it with radiation therapy as an adjuvant (CRT) may improve the survival of patients with incompletely resected tumors. This must still be demonstrated in a prospective trial. Neoadjuvant CRT is a promising treatment but still under

evaluation. There is no standard treatment for patients with locally advanced tumors. A strategy of initial chemotherapy (gemcitabine) followed by CRT for patients with non-progressive tumors are under evaluation in the LAP07 randomized trial [654].

Measurements of effects

CA 19-9 at cytostatic therapy

In order to investigate the use of CA19-9 serum concentration kinetics during first-line chemotherapy of pancreatic cancer as a potential predictive prognostic factor for overall survival, it was retrospectively analysed the data of 47 patients suffering from proven exocrine pancreatic cancer. The patients were treated following our concept of efficacy-orientated sequential palliative chemotherapy (EOSPC), on the basis of a short-term follow-up including CA19-9 determinations at least monthly and imaging methods CT and/or MR every 2 months. The results are in agreement with our previous reports suggesting an increase of survival of pancreatic cancer patients in relation to the number of effective treatment regimens applied. However, apart from a weak correlation between the lowest CA19-9 levels induced by the first-line therapy (as a % of the initial pretherapeutical CA19-9 levels) and progression-free survival there was no correlation between the various parameters of serum kinetics of CA19-9 in the course of the first-line therapy and overall survival of the patients. A potential correlation as reported by others seems to be confirmed in our patient group by the potential antitumoral and life-prolonging effects of the second- and third-line therapies [655].

Combination of CA 19-9, CEA, and CRP

The objective of one study was to define prognostic serum biomarkers that could serve as surrogate survival endpoints during second-line treatment for advanced pancreatic cancer. The retrospective single-center study included patients treated with second-line therapy for advanced exocrine pancreatic cancer. A pretreatment value and at least one serial measurement during the first two cycles of second-line chemotherapy for CA 19-9, CEA, CRP, and LDH had to be available in order to evaluate the prognostic role of kinetics on overall survival. A cutoff of a >20 percent increase from baseline during treatment was defined in order to form groups with suspected different outcomes. The effect of serial biomarker changes on survival was modeled by Cox proportional hazards regression in univariate and multivariate analyses. Overall, 70 patients treated with second-line therapy for advanced disease were included; 94 percent had distant metastases at treatment initiation. Median time to progression was 3 months and median survival 5 months. Univariate analysis found that an increase of >20 percent during treatment was significantly associated with a significantly worse overall survival for CA 19-9 (hazard ratio 2.00), CEA (hazard ratio 2.38), and CRP (hazard ratio 3.06). These associations remained significant within multivariate analysis for CEA (hazard ratio 2.86) and CRP (hazard ratio 3.20, $p = 0.001$). Serum biomarker kinetics might serve as useful prognostic tools during second-line chemotherapy in advanced pancreatic cancer [656].

Neoadjuvants

Borderline resectable pancreatic cancer is an emerging stage of disease defined by computed tomography criteria, patient (Katz type B), or disease characteristics (Katz type C). These patients are particularly well suited to a surgery-last strategy with induction therapy consisting of chemotherapy (gemcitabine alone or in combination) followed by chemoradiation. With appropriate selection and preoperative planning, many patients with

borderline resectable disease derive clinical benefit from multimodality therapy. The use of a standardized system for the staging of localized pancreatic cancer avoids indecision and allows for the optimal treatment of all patients guided by the extent of their disease. In one article, two case reports are presented, and the term borderline resectable pancreatic cancer is discussed [657].

A randomized phase II trial (E1200) was designed to assess toxicities and surgical resection rates in two neoadjuvant gemcitabine-based chemoradiation regimens in patients with borderline resectable pancreatic cancer. The trial was terminated early due to poor accrual. Patients with borderline resectable adenocarcinomas of the pancreas were enrolled. Arm A patients (n=10) received gemcitabine 500 mg/m² IV weekly for 6 weeks, with radiation to 50.4 Gy followed by surgical resection. Arm B patients (n=11) received preoperative gemcitabine 175 mg/m² on days 1, 5, 29, and 33, cisplatin 20 mg/m² on days 1-5 and 29-32, 5-FU 600 mg/m² on days 1-5 and 29-32, followed by radiation with continuous infusion 5-FU 225 mg/m² for 6 weeks. All patients received adjuvant gemcitabine 1,000 mg/m² weekly x 3 for five cycles. Three patients in arm A, and two patients in arm B were resected. Hematologic toxicity was comparable between the two arms except more patients in arm B developed grade 3 or 4 thrombocytopenia than those in arm A. Arm B had fewer grade 1-2 GI toxicities although more patients (45 %) experienced grade 3-4 GI toxicity. The authors concluded that this phase II trial showed that both regimens were tolerable, and resectability and survival were comparable to previous studies [658].

Neoadjuvant therapy – chemotherapy and/or radiotherapy given before surgery – aims to convert unresectable tumors into resectable tumors by shrinking the visible tumor and removing cancer cells that cannot be seen with the naked eye. Randomized phase III trials – studies in which groups of patients are randomly assigned to different interventions and specific outcomes measured – are the best way to determine whether an intervention has any clinical benefits, but no randomized phase III trials of neoadjuvant therapy for unresectable pancreatic cancer have been undertaken. Neoadjuvant treatment and reassessment may identify those patients (both initially resectable and non-resectable) presenting with rapid progressive or disseminated disease at restaging who therefore have a very poor prognosis and for whom surgery is unlikely to provide any benefit. On the other hand, there is the potential risk for tumor progression during neoadjuvant therapy, i.e. patients with initially resectable tumors might present with local or distant tumor progression at restaging, which might not have occurred in the setting of an initial tumor resection. In addition, neoadjuvant treatment protocols usually require histological confirmation before initiation of therapy, resulting in additional invasive diagnostic measures. Clearly, only randomized controlled trials can clarify which of the hypothetical advantages/disadvantages are real and which ones are not. There is only one phase III randomized controlled trial being carried out comparing neoadjuvant therapy and surgery with surgery alone (NCT00335543). This multicenter trial has been recruiting patients since June 2003 and has currently enrolled less than a third of the originally planned 254 patients. Due to the exceedingly slow recruitment, the study will be terminated before reaching the target population. However, there is a strong rationale for a neoadjuvant approach, since a relevant percentage of pancreatic cancer patients present with non-metastatic but locally advanced disease and microscopic incomplete resections are common. In a substantial number of patients (approximately 30 to 40 %) the disease is considered “locally advanced” at the time of diagnosis. This group of patients has been intensively discussed during the last years and neoadjuvant therapies have been proposed to achieve better local tumor control or tumor down-staging with a subsequent potentially resectable tumor. The objective of one analysis was to systematically review studies concerning the effects of neoadjuvant therapy on tumor response, toxicity, resection, and survival percentages in pancreatic cancer. Trials were identified by searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1966 to December 2009 as well as through reference lists of articles and proceedings of major meetings. Retrospective and prospective studies analyzing

neoadjuvant radiochemotherapy, radiotherapy, or chemotherapy of pancreatic cancer patients, followed by re-staging, and surgical exploration/resection were included. Two reviewers independently extracted data and assessed study quality. Pooled relative risks and 95 percent confidence intervals were calculated using random-effects models. Primary outcome measures were proportions of tumor response categories and percentages of exploration and resection. A total of 111 studies (n=4,394) including 56 phase I-II trials were analyzed. A median of 31 (interquartile range, IQR, 19-46) patients per study were included. Studies were subdivided into surveys considering initially resectable tumors (group 1) and initially non-resectable (borderline resectable/unresectable) tumors (group 2). The main agents were gemcitabine, 5-FU (and oral analogues), mitomycin C, and platinum compounds. In the trials that used only one regimen (n=79), 43 (54 %) were performed using 5-FU or its oral analogues. 5-FU monotherapy was given in 14 (18 %) of the studies. Thirty-six (46 %) of the studies used a gemcitabine-based regimen, and of those, 18 (22.8%) studies applied gemcitabine monotherapy. 5-FU and gemcitabine combinations were used in 3 studies. Several studies compared different schemes or agents. Five studies were performed comparing gemcitabine with 5-FU or capecitabine, two studies comparing gemcitabine with cisplatin, two gemcitabine with 5-FU/cisplatin, and another three gemcitabine with 5-FU/mitomycin C. A further 16 studies included different agents and combinations (some for only few patients). Twelve trials included taxanes (docetaxel/paclitaxel) in different combinations or as monotherapy (n=3). Five of the 107 studies included antibodies or tyrosine kinase inhibitors (bevacizumab, cetuximab, erlotinib) in the chemotherapeutic regimen. There were 44 studies using single agents (alone or in comparison) and 48 studies using combination therapies. In 15 studies both single agents and combination therapies were utilized. In 104 of the 111 studies (94 %) patients received neoadjuvant radiotherapy. In three studies the exact radiation dose was not given. Doses applied ranged from 24 Gy to 63 Gy. In 52 of the 104 studies that included radiotherapy the patients received doses between 45 and 50.4 Gy. In 14 studies different doses and radiation schedules were compared. Most patients received 1.8 Gy/fraction (50/104 studies), 2 Gy/fraction (15/104), or 3 Gy/fraction (10/104). In 13 studies intraoperative radiation (IORT) was applied with doses between 10 and 30 Gy. Since in most of those studies only few patients received IORT, this aspect was not further analyzed. Data regarding treatment-related toxicity were available for 63 of 111 studies. For subsequent analysis, only severe (grade 3/4) toxicity (National Cancer Institute Common Toxicity Criteria; ctep.cancer.gov) was taken into account. Grade 3/4 toxicity for neoadjuvant therapy was estimated at 29 percent (95 % confidence interval 23 % to 36 %) for all patients and was comparable for initially resectable (26 %; confidence interval 16 % to 38 %) and patients with non-resectable tumors ("non-resectable tumor patients") (31 %; 95 % confidence interval 22 % to 41 %). Recent randomized controlled trials for adjuvant therapy report grade 3/4 toxicity rates for chemotherapy of 8-22 percent (only neutropenia) and 15 percent (all toxicity). The reported grade 3/4 toxicity rates for radiochemotherapy were 9-58 percent (only hematological toxicity) and 22-79 percent (all toxicity). Tumor response frequency for neoadjuvant chemo- and/or radiation therapy was evaluated in the different studies according to either radiographic or clinical response evaluation before exploration or histopathological response after resection. Six studies (5 %) explicitly stated that the RECIST criteria were utilized. In 44 studies (40 %) the criteria to assess tumor response were clearly stated, whereas in 61 studies (55 %) criteria were either not clearly defined or not stated. For the whole study population the estimated fraction of patients with complete response was 4 percent (95 % confidence interval 3 % to 5 %) and with partial response 29 percent (95 % confidence interval 25 % to 34 %). Stable disease was averaged to 44 percent (95 % confidence interval 38 % to 50 %) in all patients and tumor progression under therapy occurred by estimation in 21 percent (95 % confidence interval 17 % to 25 %) of the patients. Interestingly the pooled percentages did not vary much in the two groups of initially deemed resectable and non-resectable tumor patients. Averaged complete/partial response probabilities were 4 percent (95 % confidence interval 2 to 6 %)/31 percent (95 % confidence interval 21 to 41 %) and 5 percent (95 % confidence interval 4 to 6 %)/30 percent (95 % confidence interval 25 to 36 %)

for groups 1 and 2, respectively; whereas progressive disease fraction was estimated to 21 percent (95 % confidence interval 17 to 25 %) and 21 percent (95 % confidence interval 15 to 28 %). In group 1, resectability was estimated to 74 percent (95 % confidence interval 66 to 81 %) compared to 33 percent (95 % confidence interval 26 to 41 %) in group 2. Higher resection-associated morbidity and mortality rates were observed in group 2 versus group 1 (27 %; 95 % confidence interval 21 to 33 % vs 39 %; 95 % confidence interval 30 to 49 %; and 4 %, 95 % confidence interval 2 to 6 % vs 7 %; 95 % confidence interval 5 to 10 %). Comparing tumor response frequencies for patients treated with mono chemotherapy (n=44) versus combination chemotherapy (n=48) revealed complete and partial responses of 2 percent (95 percent confidence interval 1 % to 3 %) and 26 percent (95 % confidence interval 20 % to 32 %) versus 5 percent (95 % confidence interval 4 % to 7 %) and 35 % (95 % confidence interval 29 % to 41 %). Operations performed included explorative laparotomies, palliative bypass procedures, and curative resections, e.g. partial pancreaticoduodenectomies, distal pancreatectomies, and total pancreatectomies. Studies were analyzed for patients explored and resected after restaging. All 111 studies included data for resection. Seven studies (6.3%) explicitly used the NCCN guidelines of resectability for non-metastatic pancreatic cancer. Forty-five studies (41 %) clearly defined the resectability criteria assessing most often the vascular involvement or classified the resectability according to the maximal tumor dimension. In 59 studies (53 %), resectability criteria were not clearly stated (e.g. judged by single surgeons or an interdisciplinary team) or not stated at all. In group 1 including the patients who were staged to be resectable before neoadjuvant treatment resectability estimated to 74 percent (95 % confidence interval 66 % to 81 %) whereas in group 2 including the patients who were staged non-resectable before treatment the averaged probability for resectability was 33 percent (95 % confidence interval 26 % to 41 %). In the assessable studies the percentage of exploration for the entire group was 70 percent (95 % confidence interval 62 % to 76 %) and 78 percent (95 % confidence interval 72 % to 83 %) of these patients were resected. Of the patients deemed resectable before treatment, 88 percent (95 % confidence interval 83 % to 92 %) were explored after restaging, and of those 86 percent (95 % confidence interval 79 to 91 %) could be resected. In group 2, 47 percent (95 % confidence interval 37 % to 57 %) of the patients were explored. Of them, 70 percent (95 % confidence interval 61 % to 78 %) could be resected successfully. Interestingly the estimated fraction of R0 resections were comparable between patients in group 1 (82 %; 95 percent confidence interval 73 % to 90 %) and patients in group 2 (79 %; 95 % confidence interval 72 % to 85 %). Data regarding morbidity and mortality following neoadjuvant treatment and pancreatic resection were presented in 50 and 85 of 111 studies, respectively. Perioperative morbidity was estimated at 34 percent (95 % confidence interval 28 % to 40 %) for all patients, which is within the range of reported morbidity data of 30-55 percent for major pancreatic (head) resections. In-hospital mortality after neoadjuvant treatment and tumor resection was estimated at 5.3 percent (95 % confidence interval 4.1% to 6.8%) for all patients. Interestingly, morbidity and mortality rates were estimated higher in the group of initially non-resectable versus resectable tumor patients (morbidity: 39 % vs 27 %, mortality: 7.1 % vs 3.9 %). Survival times for the individual studies were calculated from the time of diagnosis/start of neoadjuvant therapy in 47 trials and from surgery/resection in 4 trials. In 60 studies no detailed information regarding survival or survival calculations were provided. The longest median survival (23 months, range 12-54 months) was estimated for the group of initially staged resectable tumor patients who were resected after neoadjuvant treatment. The initially non-resectable staged patients reached an estimated median survival of 21 (range 9-62) months following resection. The estimated median survival for the entire group of resected patients was 22 (range 9-62) months. As expected, the median survival of the entire group of patients who did not undergo resection was shorter with 10 (range 6-21) months. The patients who were initially classified as resectable and did not undergo resection after pretreatment survived an estimated median of 8 (range 6-14) months, compared to 10 (range 6–21) months of patients initially diagnosed as unresectable who did not undergo resection. Estimated 1- and 2-y survival probabilities for resected patients in group 1 were 78 percent and 47 percent and for group 2 80 percent and 50 percent. In the

analysis 47 percent of the patients initially staged unresectable underwent surgical exploration. Of them, 70 percent could be resected successfully, leading to a resectability rate after neoadjuvant treatment in this group of patients of a relevant 33 percent (with comparable R0 resection rates as in the group of initially resectable tumor patients). Morbidity and mortality rates following resection were estimated higher in this group of patients as compared to initially resectable tumor patients, most likely reflecting a more extensive/aggressive surgical approach rather than effects of neoadjuvant therapy. However, resectability criteria and especially definitions of borderline resectable/unresectable tumors were variable. Thus, in more than 50 percent of the studies resectability criteria were not or not clearly stated, thereby constituting a potential source of bias. For the group of patients who present with locally advanced/unresectable disease, the median survival was 6-11 months. Similarly, in the analysis, patients initially diagnosed as unresectable who were not resected had a median survival of 10 months. In contrast, the 33 months resected patients of the initially non-resectable tumor patients had an estimated median survival of 21 months, which is within the range of pancreatic cancer patients with primary resection and adjuvant therapy. Patients who respond to chemotherapy have a better prognosis than those who do not. Therefore, one can only speculate about the survival time in responding patients if they were not resected. However, the fact that this subgroup of responding patients has the same median survival as patients who underwent immediate resection suggests that the increase in survival time for these patients can probably be attributed to the better treatment (resection) and is not due to patient selection. It was concluded that the most important findings are that in the group of resectable tumor patients, resection and survival rates after neoadjuvant therapy are similar to the ones observed in primarily resected tumor that are treated by adjuvant therapy. Thus, in this group of patients, the current data do not point to an obvious advantage of neoadjuvant therapy. In contrast, in patients initially staged locally advanced/unresectable, approximately one third of the patients can be resected following neoadjuvant therapy with comparable survival rates as patients who were staged as resectable before treatment. Due to the heterogeneity of applied protocols, data regarding the optimal chemotherapeutic and radiotherapeutic regimen cannot be extrapolated; however, the data suggest that combination chemotherapies result in higher response rates, which is reflected by higher resection rates at least in the group of initially non-resectable tumor patients. Future trials have first to clearly establish the role of neoadjuvant therapy specifically in locally advanced/unresectable tumors and subsequently to define optimal treatment protocols. In addition, common definitions for resectability/non-resectability as well as for response evaluation should be applied. As of now, the available data strongly suggest that patients with locally advanced/unresectable tumors should be included in neoadjuvant protocols and subsequently be re-evaluated for resection, which is possible in a relevant number of patients [659].

Prognostic tests

Positron emission tomography (PET) is a metabolic imaging system that is widely used for the initial staging of cancer and detecting residual disease after treatment. There are limited data, however, on the use of this molecular imaging technique to assess early tumor response after treatment in pancreatic cancer. The objective of one study was to explore the relationship of early treatment response using the F-fluorodeoxyglucose (FDG) PET with surgical outcome and overall survival in patients with locally advanced pancreatic cancer. FDG-PET measurements of maximum standardized uptake value and kinetic parameters were compared with the clinical outcome. Twenty patients were enrolled in the study evaluating neoadjuvant induction chemotherapy followed by concurrent chemoradiotherapy (chemo-RT) for locally advanced pancreatic cancer. All 20 patients had prestudy PET scans and a total of fifty PET scans were performed. Among patients who were PET responders (≥ 50 % decrease in standardized uptake value after cycle 1), 100 percent (2/2) had complete surgical resection. Only 6 percent (1/16) had surgical resection in the PET nonresponders (<50 % decrease). Two patients did not have the second PET scan because of clinical

progression or treatment toxicity. Mean survival was 23 months for PET responders and 11 months for nonresponders, which was a not statistically significant difference. Similar differences in survival were also noted when response was measured using Patlak analysis. It was thus concluded that FDG-PET can aid in monitoring the clinical outcome of patients with locally advanced pancreatic cancer treated with neoadjuvant chemo-RT. FDG-PET may be used to aid patients who could have complete surgical resection as well as prognosticate patients' survival [660].

Gemcitabine plus oxaplatin

Neoadjuvant chemotherapy can facilitate pancreatic resection in patients with initially unresectable pancreatic cancer (PC). It was reported the results of a phase II trial of gemcitabine-oxaliplatin neoadjuvant chemotherapy for patients with locally advanced, nonmetastatic PC. A prospective, phase II clinical trial using neoadjuvant chemotherapy, consisting of gemcitabine (900 mg/m²) and oxaliplatin (60 mg/m²) given as intravenous infusion once a week at day 1 of each treatment cycle (NeoGemOx protocol). Patients received 6-9 cycles of chemotherapy. Those patients with sufficient tumor regression subsequently underwent pancreatic resection and were followed postoperatively to assess long-term survival. A total of 33 patients were eligible and were included in the intent-to-treat and evaluable population. On centralized review of the imaging studies, 18 patients had unresectable disease at inclusion, and 15 patients had borderline resectable PC. Eventually, 13 patients (39 %) had a curative resection after neoadjuvant therapy. The R0 resection rate was 69 percent. Median overall survival of patients who underwent tumor resection was 22 months (95 % confidence interval 14 to 30) compared with 12 months (95 % confidence interval 9 to 15) for those without resection. The median recurrence-free survival rate after resection was 10 months (95 % confidence interval 4 to 17). It was concluded that neoadjuvant gemcitabine plus oxaliplatin is well tolerated and safe. Substantive tumor regression occurs in some patients with locally advanced pancreatic treated with this neoadjuvant protocol, offering the potential for curative resection and improvement in overall survival [661].

Docetaxel-based

To assess the safety and efficacy of a new neoadjuvant chemoradiation (CRT) docetaxel-based regimen in patients with resectable adenocarcinoma of the pancreatic head or body 34 patients with histologically-confirmed resectable pancreatic adenocarcinoma were included in a prospective two-center phase II study. Radiotherapy was delivered at the dose of 45 Gy in 25 fractions of 1.8 Gy per fractions, 5 days/week, over 5 weeks. Docetaxel was administered as a 1-h intravenous (IV) infusion repeated every week during 5 weeks. The dose was 30 mg/m²/week. All patients were restaged after completion of CRT. Tumor progression was documented in 11 patients (32 %), stable disease was documented in 20 patients (59 %), and partial remission was documented in 3 patients (9 %). Twenty-three patients still with local disease at restaging underwent explorative laparotomy. Of this, 17 patients (50 %) had a curative pancreaticoduodenectomy with lymphadenectomy. Morbidity and mortality rates were 29 percent and 0 percent, respectively. Three patients (17 %) had complete histological responses and 5 patients had minimal residual disease. All resected patients (n=17) underwent R0 resection. The median and five-year survival times for the resected patients were 32 months and 41 percent, respectively. Among the resected patients, ten (59 %) died as a result of recurrent pancreatic cancer without local tumor bed recurrence. It was concluded that neoadjuvant docetaxel-based chemoradiation is well-tolerated. Resected patients had a prolonged survival time [662].

DocMitoCape

Preclinical data indicate the improvement of the antitumor activity of capecitabine by mitomycin C and docetaxel through upregulation of thymidine phosphorylase activity. Therefore, we have established a combination regimen of these drugs (DocMitoCape), which demonstrated preliminary activity especially in bile duct and pancreatic carcinoma. It was reported the safety and efficacy of the DocMitoCape regimen in pre-treated patients with gallbladder, bile duct, or pancreatic carcinoma. Treatment consisted of capecitabine (2,000 mg/m² days 1-14) in combination with docetaxel (40 mg/m² day 1) and mitomycin C (4 mg/m² day 1). Cycles were repeated on day 22. Toxicity was graded according to NCI-CTC criteria, and the antitumor activity was assessed by RECIST criteria. Twenty-eight pre-treated patients with a median age of 59 suffering from pancreatic, gallbladder, intra- (IHCCC) or extrahepatic (EHCCC) bile duct carcinoma were included. Eleven patients had received ≥ 2 lines of prior chemotherapy. A total of 183 and a median of six cycles were administered (range 1-21). The mean dose intensity was as follows (cycles 1-2/3-4; %): capecitabine 97/92, docetaxel 100/100, mitomycin C 99/100. Main adverse events grades 2/3/4 were (n): leukocytopenia 3/2/2, anemia 13/4/0, thrombocytopenia 3/1/0, nausea/vomiting 2/1/0, diarrhea 5/1/0, hand-foot-skin reaction 7/0/0. Six patients achieved partial and seven patients minor remissions, while six patients had stable disease adding to a tumor control rate of 68 percent. Median progression-free and overall survival was 4.5 (range 1.0-44.9) and 6.8 months (range 1.5-44.9), respectively, calculated from the start of treatment. In all, the DocMitoCape regimen exhibited a favorable safety profile and a high rate of tumor stabilizations in patients with pre-treated gallbladder, bile duct and pancreatic carcinoma. It might be considered after failure of standard regimens in these types of cancer [663].

Docetaxel plus radiotherapy

To assess the safety and efficacy of a new neoadjuvant chemoradiation (CRT) docetaxel-based regimen in patients with resectable adenocarcinoma of the pancreatic head or body 34 patients with histologically-confirmed resectable pancreatic adenocarcinoma were included in this prospective two-center phase II study. Radiotherapy was delivered at the dose of 45 Gy in 25 fractions of 1.8 Gy per fractions, 5 days/week, over 5 weeks. Docetaxel was administered as a 1-h intravenous (IV) infusion repeated every week during 5 weeks. The dose was 30 mg/m²/week. All patients were restaged after completion of CRT. Tumor progression was documented in 11 patients (32 %), stable disease was documented in 20 patients (59 %), and partial remission was documented in 3 patients (9 %). 23 patients still with local disease at restaging underwent explorative laparotomy. Of this, 17 patients (50%) had a curative pancreaticoduodenectomy with lymphadenectomy. Morbidity and mortality rates were 29 percent and 0%, respectively. Three patients (17 %) had complete histological responses and 5 patients had minimal residual disease. All resected patients (n=17) underwent R0 resection. The median and five-year survival times for the resected patients were 32 months and 41percent, respectively. Among the resected patients, ten (59 %) died as a result of recurrent pancreatic cancer without local tumor bed recurrence. It was concluded that the neoadjuvant docetaxel-based chemoradiation is well-tolerated. Resected patients had a prolonged survival time [664].

Adjuvants

Pancreatic adenocarcinoma is one of the most aggressive tumors, with a high potential for early dissemination and a relatively poor sensitivity to radiation therapy and cytotoxic agents. Complete resection of the tumor is currently the only curative option but only 10-15 percent of patients present with localized, potentially resectable disease at the time of diagnosis. Median overall survival for all resected patients (R0 and R1) averages between 11 and 23 months, 5-year overall survival ranges from 10 to 25 percent (R0) and 0 to 5 percent (R1),

leading to a case-fatality index of 95 percent. Despite the latest trend toward adjuvant chemotherapy with gemcitabine due to the results from the Charité Onkologie-001 trial, there is no broad consensus regarding the adjuvant regimen that should be applied. Early data from the European Study Group for Pancreatic Cancer-3(v2) trial revealed no difference in terms of overall survival between 5-fluorouracil/folinic acid and gemcitabine after resection of pancreatic cancer [665].

Survival for pancreatic ductal adenocarcinoma is low, the role of adjuvant therapy remains controversial, and recent data suggest adjuvant chemoradiation (CRT) may decrease survival compared with surgery alone. The goal of one study was to examine efficacy of adjuvant CRT in resected pancreatic adenocarcinoma compared with surgery alone. Patients with pancreatic adenocarcinoma at Johns Hopkins Hospital (n=794, 1993-2005) and Mayo Clinic (n=478, 1985-2005) following resection who were observed (n=509) or received adjuvant 5-FU based CRT (median dose 50.4 Gy; n=583) were included. Cox survival and propensity score analyses assessed associations with overall survival. Matched-pair analysis by treatment group (1:1) based on institution, age, sex, tumor size/stage, differentiation, margin, and node positivity with 248 per treatment arm was performed. Median survival was 19 months. Overall survival (OS) was significantly longer among recipients of CRT versus surgery alone (median survival 21 vs 16 months; 2- and 5-year OS 45 vs 35 %; 22 vs 16 %). Compared with surgery alone, adjuvant CRT improved survival in propensity score analysis for all patients by 33 percent, with significantly improved survival when stratified by age, margin, node, and T-stage (RR 0.57-0.75). Matched-pair analysis demonstrated OS was longer with CRT (22 vs 14 months median survival; 2- and 5-year OS 46 vs 31 %; 25 vs 12 %). It was concluded that adjuvant CRT is associated with improved survival after pancreaticoduodenectomy. Adjuvant CRT was not associated with decreased survival in any risk group, even in propensity score and matched-pair analyses. Further studies evaluating adjuvant chemotherapy compared with adjuvant chemoradiation are needed to determine the most effective combination of systemic and local-regional therapy to achieve optimal survival results [666].

Surgery followed by chemotherapy and radiation offers patients with pancreatic adenocarcinoma a chance for extended survival. In some patients, however, resection is difficult because of vascular involvement by the carcinoma, necessitating resection and grafting of the mesenterico-portal vessels. The purpose of this study was to compare outcomes between pancreaticoduodenectomy with and without mesenterico-portal vein resection in patients receiving adjuvant CRT for pancreatic adenocarcinoma. Between 1993 and 2005, 160 patients underwent pancreaticoduodenectomy with 5-FU-based adjuvant CRT followed by maintenance chemotherapy at the Johns Hopkins Hospital; 20 (13 %) of the 160 underwent vein resection. Clinical outcomes, including median survival, overall survival, and complication rates were assessed for both groups. Patients who underwent vein resection had significantly longer operative times, greater intraoperative blood loss, and longer postoperative lengths of stay. However, postoperative morbidity, median survival, and overall survival rates were similar between the two groups. Most patients (70 %) from both groups were able to complete CRT, and a subgroup analysis demonstrated no appreciable differences in terms of complications. None of the vein resection patients who received adjuvant CRT developed veno-occlusive disease or graft failure/leakage. This means that in a cohort of patients treated with adjuvant 5-FU-based chemoradiotherapy at the Johns Hopkins Hospital, having a vein resection at the time of pancreaticoduodenectomy resulted in similar complication rates and survival. These data support the feasibility and safety of adjuvant chemoradiotherapy in patients undergoing vein resection at the time of pancreatoduodenectomy [667].

Standardization of surgical reports in adjuvant studies

Standardization of surgical and pathologic techniques is crucial to the interpretation of studies evaluating adjuvant therapies for pancreatic cancer (PC). To assess the degree to which treatment administered prior to enrollment of patients in trials of adjuvant therapy is quality controlled, the operative and pathology reports of patients in American College of Surgeons Oncology Group (ACOSOG) Z5031-a national trial of chemoradiation following pancreaticoduodenectomy (PD)-were rigorously evaluated. It was analyzed variables with the potential to influence staging or outcome. Eighty patients reported to have undergone R0 (75 %) or R1 (25 %) pylorus-preserving (38 %) or standard (62 %) PD were evaluated. A search for metastases was documented in 96 percent of cases. The proximity of the tumor to the superior mesenteric vein was reported in 69 percent; vein resection was required in 9 percent and lateral venorrhaphy in 14 percent. The method of dissection along the superior mesenteric artery (SMA) was described in 68 percent, being ultrasonic dissection (17 %), stapler (24 %), and clamp and cut (59 %). SMA skeletonization was described in 25 percent, and absence of disease following resection was documented in 24 percent. The surgeon reported marking the critical SMA margin in 25 percent; inking was documented in 65 percent of cases and evaluation of the SMA margin was reported in 47 percent. A range of 1-49 lymph nodes was evaluated. Only 34 percent of pathology reports met College of American Pathologists criteria. It was thus found that trials of adjuvant therapy following PD suffer from a lack of standardization and quality control prior to patient enrollment. These data suggest areas for improvement in the design of multidisciplinary treatment protocols [668].

Gemcitabine-based

The role of adjuvant chemoradiotherapy (CRT) in resectable pancreatic cancer is still debated. This randomized phase II intergroup study explores the feasibility and tolerability of a gemcitabine-based CRT regimen after R0 resection of pancreatic head cancer. Within 8 weeks after surgery, patients were randomly assigned to receive either four cycles of gemcitabine (control arm) or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to exclude a < 60 percent treatment completion and a > 40 percent rate of grade 4 hematologic or GI toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS). Between 2004 and 2007, 90 patients were randomly assigned (45:45). Patient characteristics were similar in both arms. Treatment was completed per protocol by 87 percent and 73 percent in the control and CRT arms, respectively, and grade 4 toxicity was 0 percent and 5 percent, respectively. In the CRT arm, three patients experienced grade 3-related late toxicity. Median DFS was 12 months in the CRT arm and 11 months in the control arm. Median OS was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11 % v 24 %). It was concluded that adjuvant gemcitabine-based CRT is feasible, well-tolerated, and not deleterious; adding this treatment to full-dose adjuvant gemcitabine after resection of pancreatic cancer should be evaluated in a phase III trial [669].

Prognostic marker for response to adjuvant gemcitabine

Treatment options for pancreatic ductal adenocarcinoma (PDA) typically include surgery and/or chemotherapy with gemcitabine. No reliable biomarker exists for prognosis or response to chemotherapy. Two previously proposed prognostic markers, cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF), are regulated by Hu protein antigen R (HuR), an mRNA binding protein that we have previously demonstrated to be a promising predictive marker of gemcitabine response. One study was designed to evaluate the clinical utility of HuR, COX-2, and VEGF as potential prognostic and predictive biomarkers for PDA.

A tissue microarray of 53 PDA specimens from patients who underwent potentially curative pancreatic resection was analyzed. HuR, COX-2, and VEGF status were correlated with clinicopathologic and survival data. It was also performed ribonucleoprotein immunoprecipitation assays using an HuR antibody to assess VEGF and COX-2 mRNA binding to HuR in pancreatic cancer cells. Roughly 50 percent (27/53) of patients had high cytoplasmic HuR expression. These patients had significantly worse pathologic features as assessed by T staging. Only cytoplasmic HuR status correlated with tumor T staging, whereas VEGF and COX-2 expression did not correlate with T staging. Additionally, HuR status was an unprecedented positive predictive marker for overall survival in patients treated with gemcitabine, pushing median survival over 45 months in the high cytoplasmic HuR expressing patient population compared with less than 23 months in the low cytoplasmic HuR expressing patient group for the low versus high cytoplasmic HuR expressing group. It was also validated that mRNA transcripts for both VEGF and the gemcitabine metabolizing enzyme, deoxycytidine kinase, are specifically bound by HuR in pancreatic cancer cells. It was concluded that HuR is a useful prognostic biomarker for PDA patients as indicated by its association with higher tumor T stage. Additionally, HuR status is a robust predictor of outcome for patients with resected PDA in the setting of adjuvant gemcitabine therapy. Finally, HuR binds to VEGF mRNA implying that HuR, in part, regulates VEGF expression in PDA [670].

Gemcitabine versus 5-fluorouracil plus folinic acid

Adjuvant fluorouracil has been shown to be of benefit for patients with resected pancreatic cancer. Gemcitabine is known to be the most effective agent in advanced disease as well as an effective agent in patients with resected pancreatic cancer. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial, an open-label, phase 3, randomized controlled trial conducted in 159 pancreatic cancer centers in Europe, Australasia, Japan, and Canada. Included in ESPAC-3 version 2 were 1088 patients with pancreatic ductal adenocarcinoma who had undergone cancer resection; patients were randomized between 2000 and 2007 and underwent at least 2 years of follow-up. Patients received either fluorouracil plus folinic acid (folinic acid, 20 mg/m², intravenous bolus injection, followed by fluorouracil, 425 mg/m² intravenous bolus injection given 1-5 days every 28 days) (n=551) or gemcitabine (1000 mg/m² intravenous infusion once a week for 3 of every 4 weeks) (n=537) for 6 months. Primary outcome measure was overall survival; secondary measures were toxicity, progression-free survival, and quality of life. Final analysis was carried out on an intention-to-treat basis after a median of 34 (interquartile range, 27-43) months' follow-up after 753 deaths (69 %). Median survival was 23 (95 % confidence interval 21 to 25) months for patients treated with fluorouracil plus folinic acid and 24 (95 % confidence interval 21 to 26) months for those treated with gemcitabine (hazard ratio, 0.94; 95 % confidence interval 0.81 to 1.08). Seventy-seven patients (14 %) receiving fluorouracil plus folinic acid had 97 treatment-related serious adverse events, compared with 40 patients (78 %) receiving gemcitabine, who had 52 events, which was a statistically significant difference. There were no significant differences in either progression-free survival or global quality-of-life scores between the treatment groups. The authors concluded that compared with the use of fluorouracil plus folinic acid, gemcitabine did not result in improved overall survival in patients with completely resected pancreatic cancer but was less toxic [671].

Gemcitabine plus radiotherapy

A randomized phase II intergroup study explores the feasibility and tolerability of a gemcitabine-based chemoradiotherapy (CRT) regimen after R0 resection of pancreatic head cancer. Within 8 weeks after surgery, patients were randomly assigned to receive either four cycles of gemcitabine (control arm) or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to

exclude a < 60 percent treatment completion and a > 40 percent rate of grade 4 hematologic or GI toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS). Between 2004 and 2007, 90 patients were randomly assigned (45 to 45). Patient characteristics were similar in both arms. Treatment was completed per protocol by 87 percent and 73 percent in the control and CRT arms, respectively, and grade 4 toxicity was 0 percent and 5 percent, respectively. In the CRT arm, three patients experienced grade 3-related late toxicity. Median DFS was 12 months in the CRT arm and 11 months in the control arm. Median OS was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11 % vs 24 %). It was concluded that adjuvant gemcitabine-based CRT is feasible, well-tolerated, and not deleterious [672].

S-1

The aim of one study was to assess the feasibility of using S-1 as adjuvant chemotherapy after the resection of pancreatic cancer. S-1 was initially administered orally at a dose of 50 mg twice daily for 14 days, followed by a rest period of seven days to complete one course. Administration was repeated with dose escalation in each cycle until the recommended dose (80 mg/m², maximum 120 mg/day), unless grade 3 adverse events were observed. Administration was planned to continue at least 6 months (eight courses). Eighteen patients who had undergone resection of pancreatic adenocarcinoma were enrolled in this study. The recommended dose could be administered to 12 patients (67 %), and 80 percent of the recommended dose was given to five patients (28 %). Although grade 3 anemia occurred in one patient, grade 4 hematologic adverse events were not observed. Grade 3 cutaneous toxicity (hand-foot syndrome) was observed in two patients. The cumulative relative total administered dose rate of S-1 was 0.86. The 3-year relapse-free survival rate was 31 percent, and the median overall survival time was 25 months. It was concluded that long-term postoperative administration of S-1 at the recommended dose is safe and appears to be a promising method of adjuvant chemotherapy [673].

Portal infusion chemotherapy

It was retrospectively assessed the benefits of 5-fluorouracil (5-FU)- and heparin-based portal infusion chemotherapy combined with systemic administration of mitomycin C (MMC) and cisplatin (CDDP) for 4 weeks following surgery (PI4W). The goal was to determine if this treatment prevented liver metastasis and improved survival for patients with potentially curative resection of pancreatic cancer. Sixty-eight patients who underwent pancreatectomy from 1995 to 2007 were treated. Of these cases, 22 patients received portal infusion with 5-FU (250 mg/day) for 2 weeks (PI2W) following surgery, while 25 patients received PI4W therapy (250 mg/day of 5-FU with 2,000 IU/day of heparin everyday for 4 weeks, 4 mg MMC on days 6, 13, 20, 27, and 10 mg CDDP on days 7, 14, 21, 28). The remaining 21 patients were treated without adjuvant therapy during the perioperative period. All patients except one completed the portal infusion chemotherapy without toxicity. The cumulative liver metastasis-free survival rate in the PI4W group was significantly higher than those in the other two groups. Furthermore, in the PI4W group, 3-year survival was 92 percent and 5-year survival was 71 percent, rates which were significantly better than those observed in the other two groups. It was concluded that PI4W therapy after surgery is feasible and could become a promising adjuvant therapy in patients with potentially curative resection of pancreatic cancer [674].

IORT

To retrospectively analyze the results of intraoperative radiotherapy (IORT) with or without external beam radiotherapy (EBRT) for resected pancreatic cancer the records of 210

patients treated with gross complete resection (R0: 147 patients; R1: 63 patients) and IORT with or without EBRT were reviewed. One hundred forty-seven patients (70 %) were treated without EBRT and 114 patients (54 %) were treated in conjunction with chemotherapy. The median doses of IORT and EBRT were 25 Gy (range, 20-30 Gy) and 45 Gy (range, 20-60Gy), respectively. The median follow-up of the surviving 62 patients was 26 months (range, 3-91 months). At the time of this analysis, 150 of 210 patients (71 %) had disease recurrences. Local failure was observed in 31 patients (15 %), and the 2-year local control rate in all patients was 84 percent. The median survival time and the 2-year actuarial overall survival (OS) in all 210 patients were 19 months and 42 percent, respectively. Patients treated with IORT and chemotherapy had a significantly more favorable OS than those treated with IORT alone. On univariate analysis, chemotherapy use, degree of resection, CA 19-9, and pathological N stage had a significant impact on OS and on multivariate analysis; these four factors were significant prognostic factors. Late gastrointestinal morbidity of NCI-CTC Grade 4 was observed in 7 patients (3 %). The authors concluded that IORT yields an excellent local control rate for resected pancreatic cancer with few frequencies of severe late toxicity, and IORT combined with chemotherapy confers a survival benefit compared with that of IORT alone [675].

ERBT

The benefit of adjuvant radiotherapy (RT) for resected pancreatic adenocarcinoma remains controversial after randomized clinical trials. In this national-level US study, a propensity score (conditional probability of receiving RT) was used to adjust for potential confounding in nonrandomized designs from treatment group differences. Patients were identified from the Surveillance, Epidemiology, and End Results (SEER) registry (1988-2005 dataset). Multivariate analyses to determine the effect of RT on overall survival were performed using propensity-adjusted Cox proportional hazards and Kaplan-Meier analyses. In total, 5676 patients with resected pancreatic adenocarcinoma were identified, and 41 percent of those patients had received adjuvant RT. Univariate significant predictors of survival included age, race, marital status, disease stage, tumor size, tumor extension, tumor grade, lymph node status, year of diagnosis, type of resection, and receipt of RT. In a Cox model, significant independent predictors of improved survival included white race, married status, earlier stage, smaller tumors, well differentiated tumors, negative lymph node (N0) status, recent diagnosis, and receipt of RT. In a propensity-adjusted proportional hazards regression, the benefit of adjuvant treatment that included RT remained significant after adjusting for the likelihood of receiving RT (hazard ratio, 0.77; 95 % confidence interval, 0.71 to 0.84). Within all 5 propensity strata, Kaplan-Meier survival differed significantly (lowest vs highest strata and middle stratum vs a "pseudorandom" probability of RT). It was concluded that adjuvant radiotherapy for resected pancreatic adenocarcinoma was associated with a significant survival advantage in a large national database, even after using propensity score methods to adjust for differences between treatment groups [676].

Stereotactic body radiotherapy

The aim of this study was to evaluate the role of stereotactic body radiotherapy (SBRT) as adjuvant therapy for resected pancreatic adenocarcinoma with close or positive margins. Between 2006 and 2010, 24 patients were treated with adjuvant SBRT following surgical resection. Eight (33 %) patients had close margins of 1-2.5 mm to the retroperitoneal, vascular structures, and periduodenal adipose tissue. Sixteen (67 %) patients had positive margins at retroperitoneal margin and vascular structures. Twenty-three patients received 24 Gy (20-24 Gy) in one fraction, and one had 30 Gy in three fractions. The median target volume was 11 cc (4.5-30 cc). Eighteen patients were treated with the Cyberknife® Robotic Radiosurgery System and six patients were treated with Trilogy intensity-modulated radiosurgery. Kaplan-Meier survival analyses were used to estimate freedom-from-local-

progression (FFLP), and overall survival (OS) rates. PET/CT or CT was used to monitor disease recurrence following SBRT. The median follow-up for all patients was 13 months (1-40 months), and among surviving patients it was 16 months (2-40 months). The FFLP rates at 6 months, 1 and 2 years were 95 percent, 66 percent, and 44 percent, respectively. Overall, FFLP was achieved in seven (88 %) patients with close margins, and 10 (63 %) with positive margins. After SBRT, 19 patients resumed or started a 6-month course of gemcitabine-based chemotherapy at a median interval of 18 days (range, 9-31 days) post-SBRT. The median OS was 27 months and the 1- and 2-year OS rates were 80 percent and 57 percent, respectively. Of the 24 patients, 12 (50 %) developed distant metastases of whom two (25 %) had close margins and 10 (63 %) had positive margins. Ten patients (42 %) were free of progression at last follow-up (range, 3-40 months). Three patients (13 %) had grade 1-2 acute GI toxicities, and two patients (8 %) had grade 1 and 2 late toxicities. No patients experienced grade 3 or 4 toxicity, including bowel perforation, secondary to SBRT. The data suggest that adjuvant SBRT for resected pancreatic cancer can be achieved with minimal toxicity. This shorter treatment course allowed initiation of systemic chemotherapy shortly after the completion of SBRT [677].

Prognostic markers for effect of medical therapy

The objective of one study was to define prognostic serum biomarkers that could serve as surrogate survival endpoints during second-line treatment for advanced pancreatic cancer. This retrospective single-center study included patients treated with second-line therapy for advanced exocrine pancreatic cancer. A pretreatment value and at least one serial measurement during the first two cycles of second-line chemotherapy for CA 19-9, CEA, CRP, and LDH had to be available in order to evaluate the prognostic role of kinetics on overall survival. A cutoff of a >20 percent increase from baseline during treatment was defined in order to form groups with suspected different outcomes. The effect of serial biomarker changes on survival was modeled by Cox proportional hazards regression in univariate and multivariate analyses. Overall, 70 patients treated with second-line therapy for advanced disease were included; 94 percent had distant metastases at treatment initiation. Median time to progression was 3 months and median survival 5 months. Univariate analysis found that an increase of >20 percent during treatment was significantly associated with a worse overall survival for CA 19-9 (HR 2.00), CEA (HR 2.38), and CRP (HR 3.06). These associations remained significant within multivariate analysis for CEA (HR 2.86) and CRP (HR 3.20). Serum biomarker kinetics might serve as useful prognostic tools during second-line chemotherapy in advanced pancreatic cancer [678].

CA 19-9

To investigate the prognostic value of quality of life (QOL) relative to tumour marker carbohydrate antigen (CA) 19-9, and the role of CA 19-9 in estimating palliation in patients with advanced pancreatic cancer receiving chemotherapy. CA 19-9 serum concentration was measured at baseline and every 3 weeks in a phase III trial (SAKK 44/00-CECOG/PAN.1.3.001). Patients scored QOL indicators at baseline, and before each administration of chemotherapy (weekly or bi-weekly) for 24 weeks or until progression. Prognostic factors were investigated by Cox models, QOL during chemotherapy by mixed-effect models. Patient-rated pain and tiredness were independent and significant predictors for survival, although less prognostic than CA 19-9. Baseline CA 19-9 did not predict QOL during chemotherapy, except for a marginal effect on pain. Mean changes in physical domains across the whole observation period were marginally correlated with the maximum CA 19-9 decrease. Patients in a better health status reported the most improvement in QOL within 20 days before maximum CA 19-9 decrease. They indicated substantially less pain and better physical well-being, already, early on during chemotherapy with a maximum CA 19-9

decrease of ≥ 50 percent versus < 50 percent. It was concluded that in advanced pancreatic cancer, pain and tiredness are independent prognostic factors for survival, although less prognostic than CA 19-9. Quality of life improves before best CA 19-9 response but the maximum CA 19-9 decrease has no impact on subsequent QOL. To estimate palliation by chemotherapy, patient's perception needs to be taken into account [679].

ERCC1

Increased knowledge about the treatment of pancreatic cancer has influenced the management of locally advanced and metastatic disease. The impact on overall survival (OS) of second-line therapy has not been clarified and the use of platinum salts and/or fluoropyrimidines is hotly debated. It is the hope that future treatment can be tailored to predict chemosensitivity in order to improve outcomes in patients with locally advanced and metastatic pancreatic cancer. Since DNA-damaging agents could be one therapeutic option, a retrospective multicenter study was performed to evaluate the efficacy of salvage treatment with the hypothesis that levels of the DNA repair gene excision repair cross complementing 1 (ERCC1) could influence OS. In a population of 160 patients treated with fluoropyrimidine-based second-line chemotherapy, expression levels of ERCC1 were determined by immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR). In 108 patients with locally advanced and metastatic pancreatic cancer treated with either fluoropyrimidines and platinum salts (group A=58) or fluoropyrimidines alone (group B=50), ERCC1 levels were correlated with OS, time to progression and response to chemotherapy. Median survival was significantly higher in group A with low ERCC1 levels (12 vs 10 months) (median follow-up 24 months). Moreover in the same group, a trend towards longer time to progression was observed. No differences in OS were observed when ERCC1 was studied (low versus high) in patients not treated with platinum salts. On multivariate analysis of pretreatment prognostic factors, ERCC1 emerged as an independent predictive factor for OS. The results of the study indicate that ERCC1 may predict survival in pancreatic cancer patients treated by platinum and fluoropyrimidine as second-line chemotherapy [680].

Gemcitabine

Gemcitabine monotherapy has become a standard chemotherapy for advanced and metastatic pancreatic cancer since the late 1990s. Because of the advancement in the molecular understanding of this malignant disease for years, many drugs including monoclonal antibody against epidermal growth factor receptors (EGFRs; cetuximab) and tyrosine kinase inhibitors (erlotinib) that inhibit specific mutations present in pancreatic cancer have been developed and investigated in clinical trials. One meta-analysis tried to overcome the statistical limitations of the individual trials and evaluates whether gemcitabine-based targeted agent therapy can further improve treatment efficacy. A comprehensive literature search was performed to identify all randomized controlled trials (RCTs). Trials were identified by systematically searching the electronic databases MEDLINE, EMBASE, and conference proceedings (American Society of Clinical Oncology, ASCO, and the European Cancer Conference) without language restriction. The search used the following key words: pancreatic cancer limited by randomized controlled trial and humans. References of eligible studies and previous reviews were also scrutinized for any other relevant trials. The latest search was done in September 2008. Randomized controlled trials were selected based on titles, abstracts, and full text; the reference lists of all traced articles and general reviews of this topic were examined manually. Trials were included according to the following criteria: (a) RCT, (b) comparing gemcitabine-based targeted agent therapy with gemcitabine monotherapy, and (c) trials reporting available data (e.g. disease progression time, survival time, and the objective tumor response). Subsequently, all trials were excluded if the gemcitabine-based targeted agent therapy was performed as adjuvant or neoadjuvant

treatment. Data from each eligible study including authors, year of publication, number of patients, baseline characteristics, median overall survival (OS), progression-free survival (PFS), overall response rate, hazards ratio (HR) and their 95 % confidence interval (CI), and adverse events were extracted by two independent reviewers using a data extraction form developed at the time of the project protocol. Any disagreements were then discussed and settled in consensus. Any data uncertainties were forwarded to the original trialists for clarification. Progression-free survival offers a direct measure of regimen activity that is not obscured by subsequent therapies. It is a more accurate surrogate survival marker in advanced pancreatic cancer. Given the poor prognosis of inoperable pancreatic cancer, the absence of effective treatment options, the better outcome of gemcitabine-based targeted agent therapy, and the acceptable toxicity, gemcitabine-based targeted agent therapy will be a good choice for inoperable pancreatic cancer. Four hundred sixteen studies could be identified but after screening the titles and abstracts, 10 studies met the inclusion criteria, and full texts were retrieved for further review. Eight RCTs involving 3199 were included and evaluated; of those, 2 are from ASCO providing the required information in abstracts and presentation slides. The pooled analysis of 8 randomized trials involving 3199 patients was included. For overall survival analysis, it demonstrates a mild survival benefit, with a 7 percent reduction in the risk of death in patients treated with gemcitabine-based targeted agent therapy compared with gemcitabine monotherapy (HR, 0.93; 95 % confidence interval 0.86 to 1.00). For PFS analysis, a total of 3025 patients were included. The analysis demonstrates a moderate but significant PFS benefit for the gemcitabine-based molecular targeted therapy (HR, 0.90; 95 % confidence interval 0.84 to 0.97). There is no heterogeneity in OS and PFS. By visual inspection of the funnel plot, no publication bias is detected. If a toxicity of grade 3 or higher was reported in more than 3 studies, these data were extracted and pool analyzed. Higher incidence of grade 3/4 was associated with the gemcitabine-based targeted agent therapy. No significant difference was observed in grade 3/4 toxicity-related neutropenia, deep venous thrombosis/pulmonary hypertension, anemia, fatigue, leukopenia, nausea, and thrombocytopenia. According to the sensitivity analysis of neutropenia, the study by Moore et al 8 was excluded. The result showed no significant benefit. According to the sensitivity analysis of anemia, the study by Kindler et al 3 was excluded. The result showed no significant benefit. According to the sensitivity analysis of leukopenia, the study by Spano et al 7 was excluded. The result showed higher incidences of leukopenia for gemcitabine-based targeted agent therapy. Four randomized trials compared the combination of gemcitabine and a targeted agent against EGFR or VEGFR (n=1022) with gemcitabine monotherapy (n=989). They included two studies in which gemcitabine was combined with an agent against EGFR and two studies in which gemcitabine was combined with an agent against VEGFR. For this group, the OS analysis demonstrates significant benefit for gemcitabine-based targeted agent therapy (HR, 0.89; 95 % confidence interval 0.81 to 0.98). For PFS analysis, it also shows significant benefit for this combination. According to the sensitivity analysis of PFS, the study by Kindler et al 3 was excluded. The result showed significant benefit for gemcitabine-based targeted agent therapy. Four randomized trials compared the combination of gemcitabine and other targeted agents (n=606) such as tipifarnib (farnesyltransferase inhibitor), CI-199 (histone deacetylase inhibitor), marimastat (matrix metalloproteinase inhibitor), and infliximab (inhibitor of tumor necrosis factor [alpha]) with gemcitabine monotherapy (n=582). Overall survival was not better in this combination group compared with that in gemcitabine monotherapy. This analysis indicated that the combination of gemcitabine and targeted agents against EGFR/VEGFR for OS was significantly better than gemcitabine monotherapy. It is the same for PFS analysis, although there was intertrial heterogeneity, which can be attributed to a heterogeneous group of patients with respect to the stage of disease. By contrast, when gemcitabine was combined with other targeted agents, no advantage can be found. This suggests that the combination of gemcitabine and agents against EGFR/VEGFR can give a clinically relevant prolongation of survival. The treatment with gemcitabine plus other targeted agents has no survival benefit in clinical practice. All targeted drugs are very

expensive. The cost-effective and overall clinical impact of targeted drugs with gemcitabine therapy on the treatment of pancreatic cancer remains to be observed further [681].

Gemcitabine is widely used as first-line chemotherapeutic drug in the treatment of pancreatic cancer. Previous experimental chemotherapy studies have shown that treatment of human pancreatic carcinoma cells with 5-fluorouracil (5-FU) alters the cellular transporter expression profile and that modulation of the expression of multidrug resistance protein 5 (MRP5; ABCC5) influences the chemoresistance of these tumor cells. It was now studied the influence of acute and chronic gemcitabine treatment on the expression of relevant uptake and export transporters in pancreatic carcinoma cells by reverse transcription-polymerase chain reaction (RT-PCR), quantitative RT-PCR, and immunoblot analyses. The specific role of MRP5 in cellular gemcitabine sensitivity was studied by cytotoxicity assays using MRP5-overexpressing and MRP5-silenced cells. Exposure to gemcitabine (12 nM for 3 days) did not alter the messenger RNA (mRNA) expression of MRP1, MRP3, MRP5, and equilibrative nucleoside transporter 1 (ENT1), whereas high dosages of the drug (20 microM for 1 hour) elicited up-regulation of these transporters in most cell lines studied. In cells with acquired gemcitabine resistance (up to 160 nM gemcitabine), the mRNA or protein expression of the gemcitabine transporters MRP5 and ENT1 was upregulated in several cell lines. Combined treatment with 5-FU and gemcitabine caused a 5- to 40-fold increase in MRP5 and ENT1 expressions. Cytotoxicity assays using either MRP5-overexpressing (HEK and PANC-1) or MRP5-silenced (PANC1/shMRP5) cells indicated that MRP5 contributes to gemcitabine resistance. Thus, the novel data not only on drug-induced alterations of transporter expression relevant for gemcitabine uptake and export but also on the link between gemcitabine sensitivity and MRP5 expression may lead to improved strategies of future chemotherapy regimens using gemcitabine in pancreatic carcinoma patients [682].

Dose-limiting toxicity

The safety and efficacy, and the dose-limiting toxicity (DLT) of the chemotherapeutic agent gemcitabine administered in conjunction with radiotherapy in patients with locally advanced pancreatic cancer are not yet established. It was now evaluated the safety and efficacy, DLT, and maximum tolerated dose of gemcitabine with concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Tumor response and time to progression were also assessed. Patients with previously untreated pancreatic cancer (n=12) received gemcitabine intravenously on days 1, 8, and 15. Concurrent radiation therapy was initiated on day 1 (40 Gy in 2 Gy/day × 20 fractions, days 1-5, 8-12, 15-19, 22-26). Patients received limited-field irradiation with three-dimensional radiotherapy. Dose escalation included dose levels 1-3 (gemcitabine 400, 600, and 800 mg/m²). No patient developed DLT in this study. Of the 12 patients, there were 11 sustained responses, 0 partial responses, and 1 progressive disease. Two patients with a sustained response underwent surgery after re-evaluation. The median progression-free survival was 8 months, not including the patients that underwent surgery. Weekly gemcitabine at a dose of 800 mg/m² with concurrent radiation therapy in patients with locally advanced pancreatic cancer was well tolerated [683].

Side effects

A 75-year-old woman was admitted because of epigastric pain. Imagings revealed cancer of the head of the pancreas. She was an HBV carrier, although no liver dysfunction was observed. Her serum HBV-DNA level was lower than 2.6. It was performed pancreatoduodenectomy for pancreatic cancer. No postoperative complication was observed. The histopathological diagnosis was tubular adenocarcinoma of the pancreas. As a postoperative adjuvant chemotherapy, gemcitabine hydrochloride (GEM) was injected at a dose of 800 mg/m² once a week. Disorientation and jaundice were observed after six doses of GEM. Blood chemistry revealed that total bilirubin and ammonia were abnormally elevated, and that blood coagulant factors were diminished. Serum HBV-DNA level was lower than 2.6. It

showed no reactivation of HBV. Abdominal CT showed no recurrence but fatty liver. Fresh frozen plasma was supplied and branched chain amino acids were injected after GEM was administration discontinued. Lactulose was also given orally. With these conservative treatments, she recovered completely [684].

A 63-year-old man with Stage IVa pancreas tail cancer was admitted for a distal pancreatectomy and splenectomy; adjuvant chemotherapy with gemcitabine was also administered. The chemotherapy was terminated after 16 courses due to hemolytic anemia, thrombocytopenia and renal dysfunction. Plasma exchange was performed; however the patient's renal function was diminished, requiring chronic hemodialysis. Physicians should be cautious of hemolytic uremic syndrome as a possible adverse reaction to gemcitabine and be aware that tests are needed for its early detection [685].

Monotherapy

Chemoradiotherapy with 5-fluorouracil has been accepted as a standard care for locally advanced pancreatic cancer; however, it has not been shown to be superior to chemotherapy alone in the gemcitabine era. One multicentre phase II study was conducted to evaluate the efficacy and safety of gemcitabine monotherapy against locally advanced pancreatic cancer in comparison with the historical data of chemoradiotherapy with 5-fluorouracil. Eligibility criteria included patients with histologically proven locally advanced pancreatic cancer, all lesions encompassed by a square of 15 cm on one side, no prior treatment, good performance status and adequate organ function. Gemcitabine was given intravenously at a dose of 1000 mg/m² over 30 min on days 1, 8 and 15, repeated every 4 weeks. The primary endpoint was 1-year survival. Expected and threshold 1-year survival were 40 and 25 percent, respectively. Between 2006 and 2007, 50 locally advanced pancreatic cancer patients were registered. The major grade 3-4 adverse events were neutropaenia (62 %), thrombocytopenia (18 %), fatigue (12 %) and infection-biliary tree (12 %). Haematological toxicity was mostly transient and there was no episode of infection with grade 3-4 neutropaenia. Up to the final follow-up in 2009, the median overall survival was 15 months with a 1-year survival of 64 percent. It was concluded that gemcitabine monotherapy demonstrated far better survival than historical data for chemoradiotherapy with 5-fluorouracil with mild toxicities. Gemcitabine could be considered as a standard treatment for locally advanced pancreatic cancer [686].

Meteronomic

The current standard of care for pancreatic cancer is weekly gemcitabine administered for 3 of 4 weeks with a 1-week break between treatment cycles. Maximum tolerated dose (MTD)-driven regimens as such are often associated with toxicities. Recent studies demonstrated that frequent dosing of chemotherapeutic drugs at relatively lower doses in metronomic regimens also confers anti-tumour activity but with fewer side effects. It was evaluated the anti-tumour efficacy of metronomic versus MTD gemcitabine, and investigated their effects on the tumour microenvironment in two human pancreatic cancer xenografts established from two different patients. Metronomic and MTD gemcitabine significantly reduced tumour volume in both xenografts. However, K(trans) values were higher in metronomic gemcitabine-treated tumours than in their MTD-treated counterparts, suggesting better tissue perfusion in the former. These data were further supported by tumour-mapping studies showing prominent decreases in hypoxia after metronomic gemcitabine treatment. Metronomic gemcitabine also significantly increased apoptosis in cancer-associated fibroblasts and induced greater reductions in the tumour levels of multiple pro-angiogenic factors, including EGF, IL-1alpha, IL-8, ICAM-1, and VCAM-1. Metronomic dosing of gemcitabine is active in pancreatic cancer and is accompanied by pronounced changes in the tumor microenvironment [687].

Gemcitabine in hepatic dysfunction

To determine the relationship between doses of gemcitabine and absolute neutrophil count and thrombocytopenia in patients with severe hepatic dysfunction (total bilirubin ≥ 4.5 mg/dL), and the relationship between doses of gemcitabine in patients with severe hepatic dysfunction and nonhematologic toxicity a retrospective chart review was conducted for patients receiving gemcitabine from 2006 through 2008. Seven patients were identified who had an elevated total bilirubin level (≥ 4.5 mg/dL) at the time they were receiving gemcitabine. All 7 patients received gemcitabine 1000 mg/m² throughout their treatment, regardless of liver function. Six patients did not experience significant hematologic toxicity warranting a dose reduction or a dose being held. One patient developed thrombocytopenia, warranting a dose being held. Gemcitabine is a chemotherapy agent frequently used for the treatment of pancreatic cancer as well as metastatic breast, lung, and ovarian cancer. To date there is limited information on dosing of gemcitabine in patients with an elevated total bilirubin. A previous study looking at lower grades of liver dysfunction suggested empiric dose reductions be made in these patients because of increased incidence of toxicity. These results indicate the possibility that no initial dose reduction is necessary for patients with liver dysfunction receiving gemcitabine; however, close monitoring of these patients is required [688].

Gemcitabine and miR-21

Curcumin induces cancer cell growth arrest and apoptosis in vitro, but its poor bioavailability in vivo limits its antitumor efficacy. It has previously been evaluated the bioavailability of novel analogues of curcumin compared with curcumin, and it was found that the analogue CDF exhibited greater systemic and pancreatic tissue bioavailability. In one study, it was evaluated the effects of CDF or curcumin alone or in combination with gemcitabine on cell viability and apoptosis in gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer cell lines. Mechanistic investigations revealed a significant reduction in cell viability in CDF-treated cells compared with curcumin-treated cells, which were also associated with the induction of apoptosis, and these results were consistent with the downregulation of Akt, cyclooxygenase-2, prostaglandin E₂, vascular endothelial growth factor, and NF-kappaB DNA binding activity. It has also been documented attenuated expression of miR-200 and increased expression of miR-21 (a signature of tumor aggressiveness) in gemcitabine-resistant cells relative to gemcitabine-sensitive cells. Interestingly, CDF treatment upregulated miR-200 expression and downregulated the expression of miR-21, and the downregulation of miR-21 resulted in the induction of PTEN. These results prompt further interest in CDF as a drug modality to improve treatment outcome of patients diagnosed with PC as a result of its greater bioavailability in pancreatic tissue [689].

Gemcitabine and Smac

Failure of chemotherapy in the treatment of pancreatic cancer is often due to resistance to therapy-induced apoptosis. A major mechanism for such resistance is the expression and activity of inhibitors of apoptosis proteins (IAP). Smac (second mitochondria-derived activator of caspase) is a mitochondrial protein that inhibits IAPs. It was shown that JP1201, a Smac mimetic, is a potent enhancer of chemotherapy in robust mouse models of pancreatic cancer. Combination of JP1201 with gemcitabine reduced primary and metastatic tumor burden in orthotopic xenograft and syngenic tumor models, induced regression of established tumors, and prolonged survival in xenograft and transgenic models of pancreatic cancer. The effect of JP1201 was phenocopied by XIAP small interfering RNA in vitro and correlated with elevated levels of tumor necrosis factor alpha protein in vivo. The continued development of JP1201 and other strategies designed to enhance therapy-induced apoptosis in pancreatic cancer is warranted [690].

Combinations with gemcitabine, overview

Previous meta-analyses showed a survival advantage with gemcitabine (GEM)-based combinations over GEM in advanced pancreatic cancer. Therefore, it would be valuable to explore the specific active regimens based on a subgroup meta-analysis. Updated data by comprehensive search of the literature from databases and conference proceedings were used. Subgroup meta-analysis compared GEM with GEM-based doublets chemotherapy in terms of 6-month overall survival (OS) and 1-year OS. Eighteen randomized controlled trials with 4237 patients were included, which were divided into five subgroups with risk ratios for overall survival:

	6 months	12 months
GEM/capecitabine	0.85 (significant)	0.94
GEM/cisplatin	0.99	0.99
GEM/5-fluorouracil	0.95	0.96
GEM/irinotecan	1.03	1.00
GEM/oxaliplatin	0.80 (significant)	0.93 (significant)

A meta-analysis of the trials with adequate information on performance status (PS) was performed in four trials with 1325 patients. Patients with a good PS did not show a survival benefit when receiving combination chemotherapy. RRs for 6-month and 1-year OS were 0.82 and 0.93. In contrast, application of combination chemotherapy to patients with a poor PS appeared to be significantly harmful. RRs were 1.17 for 6-month OS and 1.09 for 1-year OS. The meta-analysis indicated a significant survival benefit when GEM was either combined with capecitabine or oxaliplatin. On the basis of a preliminary subgroup analysis, pancreatic cancer patients with a poor PS appeared to have a worse survival benefit from GEM-based cytotoxic doublets [691].

A series of 650 patients treated between 1997 and 2007 at 10 Italian centers was analyzed to assess treatment trends and efficacy in stage III pancreatic adenocarcinoma. Data on patient characteristics, treatment and outcomes were collected. The inclusion criteria were pathological diagnosis of stage III pancreatic adenocarcinoma; age more than 18 years, Eastern Cooperative Oncology Group performance status less than 3, and no past therapy. Most patients (95 %) received up-front chemotherapy, which mainly consisted of gemcitabine alone (n=323), gemcitabine-based four-drug combinations (n=107), gemcitabine-platinum compound doublets (n=87), or intra-arterial gemcitabine-free triplets (n=57). The use of gemcitabine-platinum compound doublets increased over time (1997-2001: 2 %; 2002-2007: 21 %) whereas an inverse trend was observed for gemcitabine (71-61 %). No overall survival (OS) difference was observed between patients enrolled in clinical trials and those not enrolled. The median and 1-year OS were 10 months and 36 percent for patients treated with gemcitabine; 9 months and 37 percent for those treated with gemcitabine-free intra-arterial triplets; 13 months and 56 percent for those treated with gemcitabine-platinating agent doublets; and 16 months and 63 percent for those treated with gemcitabine-based four-drug combinations. Moreover, the median and 1-year OS were 13 months and 51 percent in patients who underwent planned consolidation chemoradiation, and 8 months and 30 percent in patients who did not. The use of a strategy consisting of a gemcitabine-platinating agent containing chemotherapy followed by consolidation chemoradiation has been increasing over time and may represent a suitable choice in the therapeutic management of stage III pancreatic adenocarcinoma [692].

Gemcitabine ± cisplatin

Single-agent gemcitabine became standard first-line treatment for advanced pancreatic cancer after demonstration of superiority compared with fluorouracil. The Gruppo Italiano Pancreas 1 randomized phase III trial aimed to compare gemcitabine plus cisplatin versus gemcitabine alone (ClinicalTrials.gov ID NCT00813696). Patients with locally advanced or metastatic pancreatic cancer, age 18 to 75 years, and Karnofsky performance status (KPS) \geq 50, were randomly assigned to receive gemcitabine (arm A) or gemcitabine plus cisplatin (arm B). Arm A: gemcitabine 1,000 mg/m² weekly for 7 weeks, and, after a 1-week rest, on days 1, 8, and 15 every 4 weeks. Arm B: cisplatin 25 mg/m² added weekly to gemcitabine, except cycle 1 day 22. Primary end point was overall survival. To have 8 percent power of detecting a 0.74 hazard ratio (HR) of death, with bilateral alpha 0.05, 355 events were needed and 400 patients planned. Four hundred patients were enrolled (arm A: 199; arm B: 201). Median age was 63, 59 percent were male, 84 percent had stage IV, and 83 percent had KPS \geq 80. Median overall survival was 8 months versus 7 months in arm A and B, respectively (HR, 1.10; 95 % confidence interval 0.89 to 1.35). Median progression-free survival was 4 months versus 4 months in arm A and B, respectively. The objective response rate was 10 percent in A and 13 percent in B, which was not statistically significant. Clinical benefit was experienced by 23 percent in A and 15 percent in B (very near statistically significant on the 5 % level). Combination therapy produced more hematologic toxicity, without relevant differences in nonhematologic toxicity. It was concluded that the addition of weekly cisplatin to gemcitabine failed to demonstrate any improvement as first-line treatment of advanced pancreatic cancer [693].

Gemcitabine plus S1

The aim of one study was to investigate the feasibility and efficacy of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. Patients with locally advanced unresectable pancreatic cancer received four cycles of induction chemotherapy consisting of 30-min intravenous infusions of gemcitabine 1,000 mg/m² on days 1 and 8 and oral S-1 40 mg/m² twice daily on days 1-14 of a 21-day cycle. Those without disease progression received chemoradiotherapy of 30 Gy in ten fractions with 250 mg/m² of gemcitabine on days 1 and 8. A total of 20 patients were treated. Median follow-up time was 431 days (range 133-1,014 days). Four cycles of induction chemotherapy were completed in 18 patients, and 16 patients received chemoradiotherapy, which was completed without delay in all. Grade 3-4 toxicities associated with induction chemotherapy were neutropenia (50 %); anemia (20 %); thrombocytopenia (10 %); febrile neutropenia (5 %); nausea (10 %); anorexia (10 %); and vomiting, fatigue, dehydration, stomatitis, and rash (5 %). Grade 3-4 toxicities among those receiving chemoradiotherapy were neutropenia (13 %) and anemia (6 %). Median progression-free survival was 8 months. Median overall survival was 14 months, with a 1-year survival rate of 54 percent. The regimen of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy used in the present study demonstrated promising activity in locally advanced pancreatic cancer [694].

In a case reported a patient with pancreatic body cancer with multiple liver metastasis in which S-1 plus gemcitabine (GEM) therapy proved to be effective. A 77-year old female was asymptomatic and diagnosed as a pancreatic body cancer with multiple liver metastases at the end of 2008 by periodical ultrasonography. After careful examination, GEM 1,200 mg/body was administered on days 1 and 15, and S-1 was administered orally at 80 mg/day for two weeks, followed by two weeks rest. Currently, at the end of the 10th course, tumor size has been reduced from 27 mm to 19 mm, and two of the five liver metastatic lesions have disappeared, while the remaining three liver lesions have been revealed as scars by CT

examination. Tumor marker levels have been remarkably decreased. Ten months from the initial diagnosis, there has been no side effect and chemotherapy is being continued [695].

One case report reveals that combination chemotherapy with S-1/gemcitabine (GEM) was very effective for a patient with unresectable pancreatic body cancer. The patient was a 72-year-old female (stage IVb). They were administered S-1 80 mg/day for 2 weeks and GEM 1,000mg/m² on day 8 and 15 followed by a 2-week recovery period. After finishing the 2 courses, there was a notable reduction in tumor size. After finishing 9 courses, the tumor could not be observed and it was judged it to be CR. Currently, at 1 year and 4 months from the initial diagnosis, there is no recurrence of tumor, and the general condition of the patient is very good. Combination chemotherapy with S-1/GEM may be useful to improve the prognosis for unresectable pancreatic cancer [696].

Costs

To assess the cost-effectiveness of chemotherapy for patients with non-resectable pancreatic cancer, it was compared two regimens containing either gemcitabine (GEM) or S-1. It was developed a decision tree that showed the clinical processes of non-resectable pancreatic cancer patients and calculated the probabilities of endpoint and life months gained (LMG) based on previously reported articles. To estimate the costs, it was analyzed medical records of 44 inpatients with non-resectable pancreatic cancer treated with GEM (n=34) or S-1 (n=10). Sensitivity analysis was used to check the robustness of the results. In the GEM group and S-1 group, costs were 1,636,393 and 985,042 yen, and LMG was 6 and 9 months, respectively. Thus, the cost-effectiveness ratio (CER) was calculated to be 272,732 and 109,449 yen/LMG, respectively, and the incremental cost effectiveness ratio (ICER) was -217,117 yen/LMG. The sensitivity analysis showed that the result was definitely robust. The findings suggest that the markedly cost-effective S-1 regimen could prolong LMG with less cost than the GEM regimen [697].

Gemcitabine ± cetuximab

There is an article specially discussing the safety, efficacy and pharmacokinetics of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer [698].

Patients with advanced pancreas cancer present with disease that is poorly responsive to conventional therapies. Preclinical and early clinical evidence has supported targeting the epidermal growth factor receptor (EGFR) signaling pathway in patients with pancreas cancer. One trial was conducted to evaluate the contribution of an EGFR-targeted agent to standard gemcitabine therapy. Cetuximab is a monoclonal antibody against the ligand-binding domain of the receptor. Patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine alone or gemcitabine plus cetuximab. The primary end point was overall survival. Secondary end points included progression-free survival, time to treatment failure, objective response, and toxicity. A total of 745 eligible patients were accrued. No significant difference was seen between the two arms of the study with respect to the median survival time (6 months or the gemcitabine plus cetuximab arm vs 6 months for the gemcitabine alone arm; hazard ratio = 1.06; 95 % confidence interval 0.91 to 1.23). Objective responses and progression-free survival were similar in both arms of the study. Although time to treatment failure was significantly longer in patients on gemcitabine plus cetuximab, the difference in length of treatment was only 2 weeks longer in the combination arm. Among patients who were studied for tumoral EGFR expression, 90 percent were positive, with no treatment benefit detected in this patient subset. It was concluded that in patients with advanced pancreas cancer, the anti-EGFR monoclonal antibody cetuximab did not improve the outcome compared with patients treated with gemcitabine alone [699].

Study results for patient-reported health-related quality of life (HRQL) outcomes were also reported. Patients completed the Brief Pain Inventory and a measure of emotional well-being (each measured on a 0 to 10 scale) at baseline and at weeks 5, 9, 13, and 17 postrandom assignment. Worst pain status was classified as palliated (worst pain scores < 5 maintained for 2 consecutive cycles) or not palliated (remaining patients). Change in emotional well-being and worst pain (exploratory analysis) were assessed over 17 weeks using generalized estimating equations with inverse probability of censoring weights. Seven hundred twenty of 766 enrolled patients contributed baseline HRQL data. The two treatment arms did not differ statistically in the percentage of patients with successful worst pain palliation. Longitudinal analyses showed significantly improved emotional well-being for patients on both arms by weeks 13 and 17. An exploratory longitudinal analysis of worst pain showed significant decreases at all time points for both arms. Significant treatment arm differences for either worst pain or emotional well-being were not observed at any of the assessment times. It was observed palliated pain and improved well-being for patients on this trial. However, these improvements were similar in both treatment arms, suggesting that the addition of cetuximab did not contribute to improvement in these HRQL outcomes [700].

Gemcitabine ± 5FU, folinic acid and cisplatin

Gemcitabine is the standard chemotherapy for patients with metastatic pancreatic adenocarcinoma. Although the 5-fluorouracil (5FU), folinic acid and cisplatin combination (LV5FU2-CDDP) is an option, the optimal order of the regimens must be determined. The first strategic phase III trial comparing LV5FU2-CDDP followed by gemcitabine versus gemcitabine followed by LV5FU2-CDDP was conducted. Patients with metastatic pancreatic adenocarcinoma, performance status (PS) 0-2, without prior chemotherapy were randomly assigned (1:1) to receive either LV5FU2-CDDP followed by gemcitabine at disease progression or toxicity (Arm A), or the opposite sequence (Arm B). 202 patients had to be included and 170 deaths had to be observed to detect an expected improvement in median overall survival (OS) from 6.5 to 10 months in Arm A (two-sided alpha = 5 % and beta = 20 %). 202 patients were included (Arm A, 102; Arm B, 100). Median age, male/female ratio, PS 0-1 and previous surgery were similar in the two arms. After a median follow-up of 44 months, median OS in Arm A was 7 months versus 8 months in Arm B, which was a not significant difference. Median progression-free survival was similar between Arms A and B. Significantly more grade 3/4 toxicities were observed when LV5FU2-CDDP was administered as a first-line treatment compared with gemcitabine: 79 percent versus 64 percent. Thus the trial did not show any strategic advantage to using LV5FU2-CDDP as a first-line treatment and the authors suggested that gemcitabine remains the standard first-line treatment. Sixty-one percent of patients were able to receive a second line of chemotherapy [701].

Gemcitabine ± bevacizumab

The combination of gemcitabine plus bevacizumab, (Avastin®; rhuMab VEGF), a monoclonal antibody targeting vascular endothelial growth factor (VEGF), produced a 21 percent response rate and a median survival of 9 months in a multicenter phase II trial in patients with metastatic pancreatic cancer. These encouraging data led Cancer and Leukemia Group B (CALGB) to conduct a double-blind, placebo-controlled, randomized phase III trial of gemcitabine/ bevacizumab versus gemcitabine/placebo in advanced pancreatic cancer patients. Eligible patients had no prior therapy for advanced disease, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, no tumor invasion of adjacent organs, and no increased bleeding risk. The primary end point was overall survival. Patients were stratified by performance status, extent of disease, and prior radiotherapy. Patients received

gemcitabine at 1,000 mg/m² over 30 minutes on days 1, 8, and 15 every 28 days and bevacizumab at 10 mg/kg or placebo on days 1 and 15 every 28 days. Between 2004 and 2006, 602 patients were enrolled onto the study and 535 were treated. Median overall survival was 6 months for gemcitabine/bevacizumab and 6 months for gemcitabine/placebo. Median progression-free survival was 4 and 3 months, respectively. Overall response rates were 13 percent and 10 percent, respectively. Patients with a performance status of 0, 1, and 2 survived a median of 8, 5, and 2 months, respectively. The only statistically significant differences in grades 3 and 4 toxicity occurred for hypertension (10 % vs 3 %) and proteinuria (5 % vs 1 %); venous thrombosis grade \geq 3 was equivalent in both arms (14 % and 15 %, respectively). It was concluded that the addition of bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer patients [702].

Bevacizumab has seen increased use in the perioperative treatment of colorectal and pancreatic cancer. Little is known, however, regarding its impact on surgical outcomes in patients undergoing resection. The objective of one review was to examine if the addition of bevacizumab to existing neoadjuvant regimens increases morbidity after cancer resection [703].

Gemcitabine plus erlotinib

National Cancer Institute of Canada Clinical Trials Group PA.3 (NCIC CTG PA.3) was a phase 3 study (n=569) that demonstrated benefits for overall survival and progression-free survival with the addition of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib to gemcitabine in patients with advanced pancreatic carcinoma (APC). Mutation status of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and EGFR gene copy number (GCN) were evaluated as predictive markers in 26 percent of patients who had tumor samples available for analysis. KRAS mutation status was evaluated by direct sequencing of exon 2, and EGFR GCN was determined by fluorescence in situ hybridization (FISH) analysis. The results were correlated with survival, which was the primary endpoint of the trial. KRAS analysis was successful in 117 patients, and EGFR FISH analysis was successful in 107 patients. KRAS mutations were identified in 92 patients (79 %), and EGFR amplification or high polysomy (FISH-positive results) was identified in 50 patients (47 %). The hazard ratio of death between gemcitabine/erlotinib and gemcitabine/placebo was 0.66 (95 % confidence interval 0.28 to 1.57) for patients with wild-type KRAS and 1.07 (95 % confidence interval 0.68 to 1.66) for patients with mutant KRAS and the hazard ratio was 0.6 (95 % confidence interval 0.34 to 1.07) for FISH-negative patients and 0.90 (95% confidence interval 0.49 to 1.65) for FISH-positive patients. It was concluded that in a molecular subset analysis of patients EGFR gene copy number and KRAS mutation status were not identified as markers predictive of a survival benefit from the combination of erlotinib with gemcitabine for the first-line treatment of APC [704].

Gemcitabine plus masitinib

To evaluate the efficacy and safety of masitinib combined with gemcitabine in patients with advanced pancreatic cancer 22 non-randomised patients with unresectable, locally advanced (n=9) or metastatic pancreatic cancer (n=13) received oral masitinib (9 mg/kg/day) combined with standard gemcitabine. All patients were naive to systemic chemotherapy or radiotherapy. The primary endpoint was time-to-progression (TTP) with efficacy and safety analyses performed on the intent-to-treat population. Secondary endpoints included overall survival (OS), as well as, subgroup analyses according to baseline disease, and performance status. Overall median TTP was 6 months (95 % confidence interval 3 to 12); 8 and 3 months, respectively, for locally advanced and metastatic patients; 6 and 1 months,

respectively, for patients with KPS [80-100] or KPS [70]. Median OS was 7 months (95 % confidence interval 5 to 17); 8 and 7 months for locally advanced or metastatic patients, respectively; 8 and 4 months in patients with KPS [80-100] or KPS [70], respectively. The 18-month observed survival rate was similar for locally advanced (22 %) and metastatic patients (23 %) and reached 28 percent for KPS [80-100] patients. The most common suspected adverse events were nausea, vomiting, rash, diarrhoea, peripheral oedema, anaemia, lymphopenia, thrombocytopenia, pyrexia, neutropenia, asthenia, leucopenia, and abdominal pain, and most were of grades 1-2 severity. The efficacy and safety of masitinib combined with gemcitabine are encouraging, with extended survival and median TTP [705].

To evaluate the efficacy and safety of masitinib combined with gemcitabine in patients with advanced pancreatic cancer. Twenty-two non-randomised patients with unresectable, locally advanced (n=9) or metastatic pancreatic cancer (n=13) received oral masitinib (9 mg/kg/day) combined with standard gemcitabine. All patients were naive to systemic chemotherapy or radiotherapy. The primary endpoint was time-to-progression (TTP) with efficacy and safety analyses performed on the intent-to-treat population. Secondary endpoints included overall survival, as well as, subgroup analyses according to baseline disease, and performance status. Overall median TTP was 6 months (95 % confidence interval 2.7 to 11.7); 8 and 3 months, respectively, for locally advanced and metastatic patients; 6 and 1 months, respectively, for patients with KPS 80-100 or KPS 70. Median overall survival was 7 months (95 % confidence interval 5 to 17); 8 and 7 months for locally advanced or metastatic patients, respectively; 8 and 4 months in patients with KPS 80-100 or KPS 70, respectively. The 18-month observed survival rate was similar for locally advanced (22 %) and metastatic patients (23 %) and reached 28 percent for KPS 80-100 patients. The most common suspected adverse events were nausea, vomiting, rash, diarrhoea, peripheral oedema, anaemia, lymphopenia, thrombocytopenia, pyrexia, neutropenia, asthenia, leucopenia, and abdominal pain, and most were of grades 1-2 severity. The authors concluded that efficacy and safety of masitinib combined with gemcitabine are encouraging, with extended survival and median TTP that support initiation of a phase 3 trial [706].

Gemcitabine plus imexone

Imexon is an aziridine-derived iminopyrrolidone which has synergy with gemcitabine in pancreatic cancer cell lines. Gemcitabine is a standard therapy for pancreatic cancer. It was performed a phase I trial of imexon and gemcitabine to evaluate safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) in patients with advanced pancreatic cancer. Patients with untreated locally advanced or metastatic pancreatic adenocarcinoma received therapy in sequential cohorts on regimen A (n=19; imexon 200 or 280 mg/m² intravenously (IV) over 30 min days 1-5, 15-19 and gemcitabine 800 or 1,000 mg/m² IV over 30 min on days 1,8,15 every 28 days) or regimen B (n=86; imexon 280-1,300 mg/m² IV over 30-60 min days 1, 8, and 15 and gemcitabine 1,000 mg/m² IV over 30 min on days 1, 8, and 15 every 28 days). One hundred five patients received 340 treatment cycles (median 2, range 1-16). Patient characteristics: median age 63, 61 percent male, ECOG PS 0/1 50 percent/50 percent, 93 percent metastatic. DLT was abdominal cramping and pain, often with transient, acute diarrhea. Best response was confirmed partial response (PR) in 11 percent, 9 percent unconfirmed PR, and 48 percent with stable disease. There was a dose proportional increase in imexon AUC across the doses tested with terminal half life 69 min at the MTD and no alteration of gemcitabine pharmacokinetics. The recommended phase II dose of imexon is 875 mg/m² with gemcitabine 1,000 mg/m. Dose-limiting toxicity was acute abdominal pain and cramping. Encouraging antitumor responses support further evaluation of this combination in advanced pancreatic cancer [707].

Gemcitabine plus glufosfamid

A dose-escalation study of glufosfamide plus gemcitabine showed that the combination could be administered safely at full doses. The purpose of one phase II study was to evaluate the safety and efficacy of this combination in chemotherapy-naive pancreatic adenocarcinoma. Eligible patients had metastatic and/or locally advanced pancreatic adenocarcinoma, Karnofsky performance status ≥ 70 , creatinine clearance (CrCL) ≥ 60 mL/min, and acceptable organ function. Patients received glufosfamide 4500 mg/m intravenous on day 1 and gemcitabine 1000 mg/m intravenous on days 1, 8, and 15 of every 28-day cycle. The primary end point was response rate. Twenty-nine patients were enrolled; 14 male, median age 58 years. Twenty-three (79 %) patients had distant metastases. Median cycles on treatment was 4 (range: 1-18+). Of 28, 5 (18 %) patients had a confirmed partial response (median duration: 8 months) and 1 had an unconfirmed partial response. Eleven patients (39 %) had stable disease. Median progression-free survival was 4 months, median overall survival was 6 months, and 1-year survival was 32 percent. Grade 3/4 neutropenia occurred in 23 (79 %) patients and grade 3/4 thrombocytopenia in 10 (34 %) patients. The CrCL fell below 60 mL/min in 10 of 27 (37 %) patients. Renal failure occurred in 4 patients. Decrease in CrCL was correlated with glufosfamide and isophosphoramidate mustard pharmacokinetic area under the curve. It was concluded that the combination of glufosfamide plus gemcitabine is active in pancreatic cancer; however, hematologic and renal toxicity were pronounced [708].

Gemcitabine plus radiotherapy

To accurately determine the maximal tolerated dose, feasibility, and antitumor activity of concurrent chemoradiotherapy including twice-weekly gemcitabine in patients with unresectable pancreatic adenocarcinoma all eligible patients with histologically proven adenocarcinoma of the pancreas were included in a phase I trial. Radiotherapy was delivered to a total dose of 50 Gy. Concurrent chemotherapy with twice-weekly gemcitabine was administered during the 5 weeks of radiotherapy, from an initial dose of 30 mg/m². The gemcitabine doses were escalated in 10 mg/m² increments in a three-plus-three design, until dose-limiting toxicities were observed. A total of 35 patients were included in the trial. The feasibility of chemoradiotherapy was high, because all the patients received the planned total radiation dose, and 26 patients (74 %) received ≥ 70 percent of the planned chemotherapy dose. The mean total delivered dose of gemcitabine was 417 mg/m² (i.e. 77% of the prescribed dose). The maximal tolerated dose of twice-weekly gemcitabine was 70 mg/m². Of the 35 patients, 13 had a partial response (37 %) and 21 had stable disease (60 %). Overall, the median survival and the 6-, 12-, and 18-month survival rates were 11 months and 82 percent, 31 percent, and 11 percent, respectively. Survival was significantly longer in patients with an initial performance status of 0 or 1. According to the authors these mature data have indicated that gemcitabine doses can be increased ≤ 70 mg/m², when delivered twice-weekly with concurrent radiotherapy. This combination shows promises to achieve better recurrence-free and overall survival [709].

Gemcitabine plus high-intensity focused ultrasound

A phase II trial was conducted to evaluate the safety and efficacy of concurrent gemcitabine and high-intensity focused ultrasound (HIFU) therapy in patients with locally advanced pancreatic cancer. Patients with localized unresectable pancreatic adenocarcinoma in the head or body of the pancreas received gemcitabine (1000 mg/m²) intravenously over 30 min on days 1, 8, and 15, and concurrent HIFU therapy on days 1, 3, and 5. The treatment was given every 28 days. Thirty-seven (95 %) of the 39 patients were assessable for response, and two cases of complete response and 15 cases of partial response were confirmed,

giving an overall response rate of 44 percent (95 % confidence interval 28 to 59 %). The median follow-up period was 17 months (range: 8-29 months). The median time to progression and overall survival for all patients were 8 months (95 % confidence interval 5 to 11 months) and 13 months (95 % confidence interval 10 to 15 months), respectively. The estimates of overall survival at 12 and 24 months were 51 percent (95 % confidence interval 37 to 65 %) and 17 percent (95 % confidence interval 6 to 28 %), respectively. A total of 16 percent of patients experienced grade 3/4 neutropenia. Grade 3 thrombocytopenia was documented in two (5 %) patients. Grade 3 nausea/vomiting and diarrhea were observed in three (8 %), and two (5 %) patients, respectively. Grade 1 or 2 fever was detected in 70 percent of patients. Twenty-eight patients (72 %) complained of abdominal pain consistent with tumor-related pain before HIFU therapy. Pain was relieved in 22 patients (79 %). In conclusion, concurrent gemcitabine and HIFU is a tolerated treatment modality with promising activity in patients with previously untreated locally advanced pancreatic cancer [710].

Gemcitabine, irinotecan and a COX-2 inhibitor

Cyclooxygenase-2 (COX-2) has been shown to be expressed in a variety of tumors including pancreatic cancer. The combination of gemcitabine and irinotecan is active in pancreatic cancer. The purpose of this study is to determine the toxicity and response rate to the addition of the selective oral COX-2 inhibitor, celecoxib, to gemcitabine and irinotecan in patients with inoperable pancreatic cancer. 21 patients with previously untreated inoperable pancreatic cancer were entered on this trial. Seven patients had localized disease, 8 had metastatic disease, and 6 patients were inevaluable. Twenty percent of the patients had a partial response and 80 percent of the patients had a stable response with a median response rate of 9 months. The median overall survival was 18 months with 80 percent of the patients achieving 1-year survival and 20 percent achieving 2-year survival. Using the FACT-PA scale to measure the quality of life (QOL), 13 of the 15 patients reported an improvement in their QOL and 2 patients reported no change. The median CA19-9 levels for the 13 patients with measurable CA19-9 values, decreased by 71 percent by cycle 2. Adverse events were acceptable and included neutropenia, thrombocytopenia, nausea, fatigue, and anemia. It was concluded that the combination of gemcitabine, irinotecan, and celecoxib is an active therapy for inoperable pancreatic cancer. A marked reduction in CA19-9 was observed in all evaluable patients by cycle 2. Toxicity is tolerable and a majority of patients reported a decrease in pain and a significant improvement in their QOL [711].

Capecitabine plus sunitinib

One open-label, phase I, dose-escalation study assessed the maximum-tolerated dose (MTD), safety, pharmacokinetics, and antitumor activity of sunitinib in combination with capecitabine in patients with advanced solid tumors. Sunitinib (25, 37.5, or 50 mg) was administered orally once daily on three dosing schedules: 4 weeks on treatment, 2 weeks off treatment (Schedule 4/2); 2 weeks on treatment, 1 week off treatment (Schedule 2/1); and continuous daily dosing (CDD schedule). Capecitabine (825, 1,000, or 1,250 mg/m²) was administered orally twice daily on days 1 to 14 every 3 weeks for all patients. Sunitinib and capecitabine doses were escalated in serial patient cohorts. Seventy-three patients were treated. Grade 3 adverse events included abdominal pain, mucosal inflammation, fatigue, neutropenia, and hand-foot syndrome. The MTD for Schedule 4/2 and the CDD schedule was sunitinib 37.5 mg/d plus capecitabine 1,000 mg/m² twice per day; the MTD for Schedule 2/1 was sunitinib 50 mg/d plus capecitabine 1,000 mg/m² twice per day. There were no clinically significant pharmacokinetic drug-drug interactions. Nine partial responses were

confirmed in patients with pancreatic cancer (n=3) and breast, thyroid, neuroendocrine, bladder, and colorectal cancer, and cholangiocarcinoma (each n=1) [712].

Gemcitabine and SBRT

Patients with nonmetastatic locally advanced unresectable pancreatic cancer have a dismal prognosis. Conventional concurrent chemoradiotherapy requires 6 weeks of daily treatment and can be arduous. It was explored the safety and effectiveness of a 3-day course of hypofractionated stereotactic body radiotherapy (SBRT) followed by gemcitabine in this population. A total of 36 patients with nonmetastatic, locally advanced, unresectable pancreatic cancer with ≥ 12 months of follow-up were included. They received three fractions of 8, 10, or 12 Gy (total dose, 24-36 Gy) of SBRT according to the tumor location in relation to the stomach and duodenum, using fiducial-based respiratory motion tracking on a robotic radiosurgery system. The patients were then offered gemcitabine for 6 months or until tolerance or disease progression. With an overall median follow-up of 24 months (range, 12-33), the local control rate was 78 percent, the median overall survival time was 14 months, the median carbohydrate antigen 19-9-determined progression-free survival time was 8 months, and the median computed tomography-determined progression-free survival time was 10 months. Of the 36 patients, 28 (78 %) eventually developed distant metastases. Six patients (17 %) were free of progression at the last follow-up visit (range, 13-30 months) as determined by normalized tumor markers with stable computed tomography findings. Nine Grade 2 (25 %) and five Grade 3 (14 %) toxicities attributable to SBRT occurred. This means that hypofractionated SBRT can be delivered quickly and effectively in patients with nonmetastatic, locally advanced, unresectable pancreatic cancer with acceptable side effects and minimal interference with gemcitabine chemotherapy [713].

Capecitabine plus radiation

Patients with locally advanced pancreatic cancer (LAPC) are most commonly managed with chemotherapy or concurrent chemoradiotherapy (CRT), which may or may not include non-involved regional lymph nodes in the clinical target volume. It was present results of CRT for LAPC using capecitabine and delivering radiotherapy to a limited radiation field that excluded non-involved regional lymph nodes from the clinical target volume. Thirty patients were studied. Patients received 50.4 Gy external beam radiotherapy in 28 fractions, delivered to a planning target volume expanded from the primary tumour and involved nodes only. Capecitabine (500-600 mg/m²) was given twice daily continuously during radiotherapy. Toxicity and efficacy data were prospectively collected. Nausea, vomiting and tumour pain were the most common grade 2 toxicities. One patient developed grade 3 nausea. The median time to progression was 9 months, with 20 percent remaining progression free at 1 year. The median overall survival was 10 months with a 1 year survival of 30 percent. Of 21 patients with imaged progression, 13 (62 %) progressed systemically, three (14 %) had local progression, two (10 %) had locoregional progression and three (14 %) progressed with both local/locoregional and systemic disease. It was concluded that CRT using capecitabine and limited field radiotherapy is a well-tolerated, relatively efficacious treatment for LAPC. The low toxicity and low regional progression rates support the use of limited field radiotherapy, allowing evaluation of this regimen with other anti-cancer agents [714].

The objective of one study was to evaluate the safety of escalating up to 55 Gy within five weeks, the dose of external beam radiotherapy to the previous tumor site concurrently with a fixed daily dose of capecitabine, in patients with resected pancreatic cancer. Patients with resected pancreatic carcinoma were eligible for this study. Capecitabine was administered at a daily dose of 1600 mg/m². Regional lymph nodes received a total radiation dose of 45 Gy

with 1.8 Gy per fractions. The starting radiation dose to the tumor bed was 50.0 Gy (2.0 Gy/fraction, 25 fractions). Escalation was achieved up to a total dose of 55.0 Gy by increasing the fraction size by 0.2 Gy (2.2 Gy/fraction), while keeping the duration of radiotherapy to five weeks (25 fractions). A concomitant boost technique was used. Dose limiting toxicity (DLT) was defined as any grade >3 hematologic toxicity, grade >2 liver, renal, neurologic, gastrointestinal, or skin toxicity, by RTOG criteria, or any toxicity producing prolonged (> 10 days) radiotherapy interruption. Twelve patients entered the study (median age: 64 years). In the first cohort (six patients), no patient experienced DLT. Similarly in the second cohort, no DLT occurred. All 12 patients completed the planned regimen of therapy. Nine patients experienced grade 1-2 nausea and/or vomiting. Grade 2 hematological toxicity occurred in four patients. The results of the study indicate that a total radiation dose up to 55.0 Gy/5 weeks can be safely administered to the tumor bed, concurrently with capecitabine (1600 mg/m²) in patients with resected pancreatic carcinoma [715].

Paclitaxel

Peritoneal metastasis is one of the major sites of disease progression of pancreatic cancer. There have been few trials in the second-line setting after gemcitabine failure because patients can hardly be candidates for chemotherapy after failure in the first-line chemotherapy, especially those with malignant ascites. The safety and efficacy of weekly paclitaxel therapy was evaluated for pancreatic cancer patients with malignant ascites in this retrospective study. The subjects of this retrospective study were 23 advanced pancreatic cancer patients with malignant ascites who received weekly paclitaxel therapy after gemcitabine failure. Paclitaxel (80 mg/m², div. for 1 h) was administered on days 1, 8 and 15, every 4 weeks. While the disease control rate was 35 percent, decrease of ascites was obtained in 30 percent of the patients and ascites control rate was 61 percent. The median survival time was 101 days. Toxicities were mild, although one treatment-related death occurred. It was concluded that weekly paclitaxel therapy may be useful treatment option for pancreatic cancer patients with malignant ascites after gemcitabine failure [716].

Docetaxel

No therapeutic standard of care exists for patients who have progressed following first-line treatment with a gemcitabine-based regimen with advanced pancreatic cancer. Approximately half of the patients failing upfront treatment present with ECOG PS 1-2 and are willing to undergo further treatment. Docetaxel activity against pancreatic cancer is reported both in the preclinical and clinical setting. One study retrospectively evaluated the role of docetaxel as second-line therapy in patients with gemcitabine-refractory disease. Between 2006 and 2009, 17 patients (median age of 61 years) with advanced pancreatic adenocarcinoma, after receiving gemcitabine-containing chemotherapy as first-line median ECOG performance status 1 and with adequate organ function, were treated with either weekly docetaxel at 25 mg/m² or 3-weekly docetaxel regimen (docetaxel at 75 mg/m² or docetaxel-gemcitabine-capecitabine or docetaxel-gemcitabine) until progressive disease. Serum CA19-9 levels were measured every 3/4 weeks and CT scans performed after every eight/nine weeks. Docetaxel dose intensity was 90 percent in the patients who received weekly docetaxel, 85 percent in docetaxel-erlotinib regimen and 65 percent in 3-weekly regimen (docetaxel-gemcitabine-capecitabine, docetaxel-gemcitabine). Only one objective response (6 %) to treatment was obtained (docetaxel-gemcitabine), while 5 patients achieved stable disease (weekly docetaxel). Median progression-free survival was 8 weeks (range: 3-16 weeks) and median survival was 4 months (range: 2-7 months). No toxicity with grade >3 associated with docetaxel was observed. Thus, docetaxel seems to have mild activity in the treatment of gemcitabine-resistant metastatic pancreatic cancer [717].

Irinotecan

One study aimed to determine the maximum tolerated dose of daily irinotecan given with concomitant radiotherapy in patients with locally advanced adenocarcinoma of the pancreas. Between 2000 and 2008, 36 patients with histologically proven unresectable pancreas adenocarcinoma were studied prospectively. Irinotecan was administered daily, 1 to 2 hours before irradiation. Doses were started at 6 mg/m² per day and then escalated by increments of 2 mg/m² every 3 patients. Radiotherapy was administered in 2 Gy fractions, 5 fractions per week, up to a total dose of 50 Gy to the tumor volume. Inoperability was confirmed by a surgeon involved in a multidisciplinary team. All images and responses were centrally reviewed by radiologists. Thirty-six patients were enrolled over a period of 8 years through eight dose levels (6 mg/m² to 20 mg/m² per day). The maximum tolerated dose was determined to be 18 mg/m² per day. The dose-limiting toxicities were nausea/vomiting, diarrhea, anorexia, dehydration, and hypokalemia. The median survival time was 13 months with a median follow-up of 54 months. The median progression-free survival time was 7 months, and 4 patients (11 %) with very good responses could undergo surgery. It was concluded that the maximum tolerated dose of irinotecan is 18 mg/m² per day for 5 weeks. Dose-limiting toxicities are mainly gastrointestinal [718].

Irinotecan and oxaliplatin (IROX)

Gemcitabine- and 5-fluorouracil (5-FU)- based chemotherapy is a commonly used adjuvant or palliative treatment for patients with pancreatic cancer. However, a standard chemotherapy regimen has yet to be developed for patients refractory to gemcitabine and 5-FU treatment. We attempted to evaluate the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a salvage treatment for patients with gemcitabine- and 5-FU- refractory pancreatic cancer. Patients with advanced pancreatic cancer who were refractory to prior gemcitabine- and 5-FU- based chemotherapy were enrolled in one study. IROX chemotherapy was administered as follows: Irinotecan, 150 mg/m² on day 1; and oxaliplatin, 85 mg/m² on day 1 over 90 min every 2 weeks. From 2006 to 2008, a total of 14 patients were administered 50 cycles of chemotherapy. The male-to-female ratio of the patient group was 11:3. These patients ranged in age from 48 to 73 years (median 66 years old). Three patients (21 %) evidenced partial responses. Four patients (29 %) exhibited stable disease. The median time to progression and overall survival time were 1.4 (95 % confidence interval 1.2 to 1.6) months and 4.1 (95 % confidence interval 2.0 to 6.2) months, respectively. Major hematologic toxicities included grade 1-2 anemia (88 %), neutropenia (36 %), thrombocytopenia (30 %), and grade 3-4 neutropenia (10 %). The most frequently detected non-hematological toxicities were grade 3 diarrheas (14 %). It was concluded that the IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who have been previously treated with gemcitabine- and 5-FU-based chemotherapy [719].

S-1

No standard salvage chemotherapy regimen has been established for patients with advanced pancreatic cancer after failure of gemcitabine-based treatment. Although a phase II study of S-1 monotherapy was conducted in patients with gemcitabine-refractory advanced pancreatic cancer, the number of patients enrolled was small. It was therefore retrospectively reviewed 84 consecutive patients who received S-1 monotherapy as a second-line treatment after gemcitabine failure between 2004 and 2008. The selection criteria in this study were age 20-75 years, ECOG performance status \leq 2 and preserved organ functions. S-1 was administered orally twice a day at a dose of 40 mg/m² for 28 days, followed by 14-day rest.

Fifty-two patients were selected for the analysis. Out of the 47/52 patients with measurable lesions, only 2 patients (4 %) showed a partial response and 15 patients (32 %) showed stable disease. The median progression-free survival was 2 months and the median overall survival was 6 months, with a 1-year survival rate of 12 percent. The common grade 3/4 toxicities were diarrhea (8 %), anorexia (6 %), fatigue (6 %), anemia (6 %) and leucopenia (4 %). It was concluded that S-1 monotherapy is marginally effective and well tolerated in the second-line setting in patients with gemcitabine-refractory advanced pancreatic cancer [720].

A 65-year-old man underwent a total gastrectomy and distal pancreatectomy for acinar cell carcinoma of the pancreas. Multiple metastatic liver lesions were found one year postoperatively. He was treated with S-1 chemotherapy over 34 months, and the tumors significantly reduced in size without severe side effects. Four years after surgery, the liver metastases increased in size, associated with pain especially in the right upper quadrant. It was then performed right hepatectomy. Peritoneal dissemination and multiple lung metastases were found 8 months after liver resection. Acinar cell carcinoma of the pancreas is a rare and highly malignant tumor, and there are few reports regarding treatment with chemotherapy [721].

The aim of one study was to investigate the effect of S-1 on the prognosis of advanced pancreatic cancer. In total, 112 patients with pancreatic cancer who received chemotherapy between 2001 and 2007 were divided into 2 groups: PreS-1 (53 patients who started chemotherapy before 2005) and PostS-1 (59 patients who started chemotherapy after 2005, the time of S-1 introduction). Patient characteristics and clinical outcomes were compared, and prognostic factors were analyzed. Patient characteristics did not significantly differ between the 2 groups. S-1 was administered as a second-line monotherapy in 6 percent of the PreS-1 group and combined with gemcitabine as a first-line therapy in 27 percent or as second-line monotherapy in 24 percent in the PostS-1 group. Both progression-free survival and overall survival improved after introduction of S-1 (median progression-free survival, 4 and 5 months which was a significant difference; median overall survival, 10 and 13 months; which also was significant in PreS-1 and PostS-1 groups, respectively). Multivariate analysis revealed that the PostS-1 group (hazards ratio, 0.52), performance status, and carcinoembryonic antigen were significant prognostic factors for survival. It was concluded that the introduction of S-1 may improve the prognosis of Japanese patients with advanced pancreatic cancer [722].

It was investigated the impact of S-1 on the prognosis of patients with gemcitabine-refractory pancreatic cancer. A total of 108 patients with gemcitabine-refractory pancreatic cancer were divided by the time of S-1 introduction in the institution: 47 patients who experienced progressive disease before 2005 (pre-S-1 group) and 61 patients showed progressive disease after 2005 (post-S-1 group). Introduction rates of second-line chemotherapy and survival were compared. Introduction rates of second-line chemotherapy were 13 percent in the pre-S-1 group and 46 percent in the post-S-1 group. Second-line chemotherapy was administered to 34 patients: 29 using S-1, 4 using 5-fluorouracil-based chemoradiation and 1 using 5-fluorouracil. The objective response rate, progression-free survival and overall survival for second-line chemotherapy with S-1 were 17 percent, 3 and 8 months, respectively. By the introduction of S-1 in the institution, residual survival was prolonged from 3 months in the pre-S-1 group to 7 months in the post-S-1 group, which was a significant increase. Overall survival from the initiation of gemcitabine was 9 months in the pre-S-1 group and 11 months in the post-S-1 group. Multivariate analysis identified the post-S-1 group (hazard ratio, 0.43), gender, performance status, liver metastasis, and lactate dehydrogenase and C-reactive protein levels at progressive disease for gemcitabine to be prognostic factors for residual survival. The authors concluded that the introduction of S-1 might improve the prognosis of patients with gemcitabine-refractory pancreatic cancer [723].

A 65-year-old man suffering from acute pancreatitis underwent MRI scanning, which revealed a low signal on the T1 and T2 sequences, and hypovascularity in arterial phase in the head of the pancreas. This corresponded to the area showing the absence of the lower common bile duct. FDG-PET was highly suggestive of pancreatic cancer (T4N1M0, Stage IVa) with lymph node metastasis. He was treated with systemic chemotherapy using gemcitabine (GEM) followed by radiotherapy. His symptoms gradually improved with a reduction in size of the primary lesion. The patient has been receiving systemic chemotherapy using S-1 without recurrence [724].

The aim of one study was to investigate the effect of S-1 on the prognosis of advanced pancreatic cancer. In total, 112 patients with pancreatic cancer who received chemotherapy between 2001 and 2007 were divided into 2 groups: PreS-1 (53 patients who started chemotherapy before 2005) and PostS-1 (59 patients who started chemotherapy after 2005, the time of S-1 introduction). Patient characteristics and clinical outcomes were compared, and prognostic factors were analyzed. Patient characteristics did not significantly differ between the 2 groups. S-1 was administered as a second-line monotherapy in 6 percent of the PreS-1 group and combined with gemcitabine as a first-line therapy in 27 percent or as second-line monotherapy in 24 percent in the PostS-1 group. Both progression-free survival and overall survival improved after introduction of S-1 (median progression-free survival, 4 and 5 months; median overall survival, 10 and 13 months; both significant differences). Multivariate analysis revealed that the PostS-1 group (hazards ratio, 0.52), performance status, and carcinoembryonic antigen were significant prognostic factors for survival. It was concluded that introduction of S-1 may improve the prognosis of Japanese patients with advanced pancreatic cancer [725].

Breath test for prediction of effect

S-1 is an oral anticancer drug containing tegafur (FT), a pro-drug of fluorouracil, combined with two modulators, 5-chloro-2,4-dihydropyridine and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1. CYP2A6 genetic polymorphism and dihydropyrimidine dehydrogenase (DPD) inhibition are important for the antitumor effect of S-1. Exploiting the usefulness of the 2-¹³C-uracil breath test (UrBT) as an indicator of DPD activity, it was examined whether the results of CYP2A6 genetic polymorphism analysis and UrBT could be used to predict the antitumor effect of S-1. Thirty-four patients with advanced or recurrent cancer (15, 16 and 3 with gastric, colorectal and pancreatic cancer, respectively) were orally administered 40 mg/m² S-1 twice daily in the morning and evening. Eighteen patients with a complete response (CR)/partial response (PR) (2 with CR, 16 with PR) and 16 with progressive disease (PD) were compared with respect to CYP2A6 genetic polymorphisms (1- vs 2-allele mutation), UrBT results, and plasma FT and 5-fluorouracil levels at 3 h after S-1 ingestion in the morning. On multivariate analysis between the CR/PR and PD groups, only the UrBT results was an independent factor of CR/PR to S-1 (95 % confidence interval 1.02 to 1.10). These results suggest that the anticancer effect of S-1 can be predicted by performing UrBT 3 h after the initial oral S-1 administration [726].

Cetuximab

To assess the efficacy and safety of cetuximab-based therapy versus non-cetuximab therapy for advanced cancer a total of 7,954 patients from 17 randomized controlled trials were identified, with 3,965 patients in the cetuximab group and 3,989 patients in the non-cetuximab group. The outcome was progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and grade 3/4 adverse events. There was a significant improvement of progression-free survival (HR 0.83; 95 % confidence interval 0.78 to 0.88), overall survival (HR 0.89; 95 % confidence interval 0.84 to 0.95), and overall response rate in

the cetuximab group (OR 1.39; 95 % confidence interval 1.22 to 1.58). In subgroup analysis, in colorectal cancer, there was a significant improvement of PFS (0.72; 95 % confidence interval 0.66 to 0.78), overall survival (0.90; 95 % confidence interval 0.81-1.00), and overall response rate in the cetuximab group (1.36; 95 % confidence interval 1.15-1.60). In pancreatic cancer, there was no difference on progression-free survival (1.11; 95 % confidence interval 0.97 to 1.28), overall survival (1.07; 95 % confidence interval 0.93 to 1.25), and overall response rate (0.94; 95 % confidence interval 0.66 to 1.33). There were higher incidences of grade 3-4 toxicity (OR 1.84), skin-related toxicity (OR 31.80), acneiform rash (OR 30.14), and hypomagnesemia (OR 6.72) in the cetuximab group. In conclusion cetuximab-based therapy did not improve progression-free survival and OS, and better ORR versus non-cetuximab therapy in pancreatic cancer. The severe adverse events should be predictable and manageable [727].

FOLFIRI

Patients with advanced pancreatic cancer failing gemcitabine-based first-line chemotherapy are still in relatively good clinical conditions and may still require second-line chemotherapy, which is frequently administered in daily clinical practice given to without solid scientific support. A retrospective survey was carried out including 40 patients with stage III or IV gemcitabine-refractory pancreatic carcinoma. Patients received standard FOLFIRI regimen biweekly until progression or unacceptable toxicity. Response evaluation criteria in solid tumors and National Cancer Institute common toxicity criteria were employed respectively for response and toxicity assessment. Six partial responses (15 %) and 14 stabilizations of disease (35 %) were recorded for a tumor growth control rate of 50 percent. The median time to progression was 4 (range, 1-7 months), and median overall survival was 6 months (range, 2-8 months). A stabilization of performance status and a subjective improvement of cancer-related symptoms were recorded in 21 patients (52 %). No correlation has been found between length of time to progression during first-line chemotherapy and length of that reported in the second-line setting or objective response. Grade 3-4 diarrhea and mucositis was observed in 15 percent and 10 percent of cases, respectively. Data presented demonstrate that the second-line FOLFIRI regimen is able to induce an objective response in a relatively small fraction of patients with gemcitabine-refractory adenocarcinoma of the pancreas. The use of second-line chemotherapy should be carefully proposed to patients with good performance status or those who had a good response to first-line therapy [728].

Kinase inhibitors

Clearly, pancreatic cancer requires new therapeutic concepts. Recently, the kinase inhibitors imatinib and gefitinib, developed to treat chronic myelogenous leukaemia and breast cancer, respectively, gave very good results. Kinases are deregulated in many diseases, including cancer. Given that phosphorylation controls cell survival signalling, strategies targeting kinases should obviously improve cancer treatment. The purpose of one review was to summarize the present knowledge on kinases potentially usable as therapeutic targets in the treatment of pancreatic cancer. All clinical trials using available kinase inhibitors in monotherapy or in combination with chemotherapeutic drugs failed to improve survival of patients with pancreatic cancer. To detect kinases relevant to this disease, it was undertaken a systematic screening of the human kinome to define a "survival kinase" catalogue for pancreatic cells. It was selected 56 kinases that are potential therapeutic targets in pancreatic cancer. Preclinical studies using combined inhibition of PAK7, MAP3K7 and CK2 survival kinases in vitro and in vivo showed a cumulative effect on apoptosis induction. It was also observed that these three kinases are rather specific of pancreatic cancer cells. In conclusion, if kinase inhibitors presently available are unfortunately not efficient for treating

pancreatic cancer, recent data suggest that inhibitors of other kinases, involved more specifically in pancreatic cancer development, might, in the future, become interesting therapeutic targets [729].

Targeted drug delivery

Effective drug delivery in pancreatic cancer treatment remains a major challenge. Because of the high resistance to chemo and radiation therapy, the overall survival rate for pancreatic cancer is extremely low. Recent advances in drug delivery systems hold great promise for improving cancer therapy. Using liposomes, nanoparticles, and carbon nanotubes to deliver cancer drugs and other therapeutic agents such as siRNA, suicide gene, oncolytic virus, small molecule inhibitor, and antibody has been a success in recent preclinical trials. However, how to improve the specificity and stability of the delivered drug using ligand or antibody directed delivery represent a major problem. Therefore, developing novel, specific, tumor-targeted drug delivery systems is urgently needed for this terrible disease. One review summarized the current progress on targeted drug delivery in pancreatic cancer and provides important information on potential therapeutic targets for pancreatic cancer treatment [730].

Sunitinib

In an open-label, phase I, dose-escalation study assessed the maximum-tolerated dose (MTD), safety, pharmacokinetics, and antitumor activity of sunitinib in combination with capecitabine in patients with advanced solid tumors. Sunitinib (25, 37.5, or 50 mg) was administered orally once daily on three dosing schedules: 4 weeks on treatment, 2 weeks off treatment (Schedule 4/2); 2 weeks on treatment, 1 week off treatment (Schedule 2/1); and continuous daily dosing (CDD schedule). Capecitabine (825, 1,000, or 1,250 mg/m²) was administered orally twice daily on days 1 to 14 every 3 weeks for all patients. Sunitinib and capecitabine doses were escalated in serial patient cohorts. Seventy-three patients were treated. Grade 3 adverse events included abdominal pain, mucosal inflammation, fatigue, neutropenia, and hand-foot syndrome. The MTD for Schedule 4/2 and the CDD schedule was sunitinib 37.5 mg/d plus capecitabine 1,000 mg/m² twice per day; the MTD for Schedule 2/1 was sunitinib 50 mg/d plus capecitabine 1,000 mg/m² twice per day. There were no clinically significant pharmacokinetic drug-drug interactions. Nine partial responses were confirmed in patients with pancreatic cancer (n=3) and breast, thyroid, neuroendocrine, bladder, and colorectal cancer, and cholangiocarcinoma (each n=1). It was concluded the combination of sunitinib and capecitabine resulted in an acceptable safety profile in patients with advanced solid tumors. Further evaluation of sunitinib in combination with capecitabine may be undertaken using the MTD for any of the three treatment schedules [731].

Bevacizumab plus erlotinib

Based on potential for additive or synergistic activity by concurrent inhibition of VEGF and EGFR, it was conducted a phase II study evaluating the combination of bevacizumab plus erlotinib in this patient population. Patients with metastatic pancreatic adenocarcinoma, ECOG performance status 0-1, and previous exposure to 1-3 systemic therapies (at least one gemcitabine-based) were eligible. Treatment consisted of bevacizumab 15 mg/kg every 21 days plus erlotinib 150 mg daily. Thirty-six patients were enrolled, including eight who had previously received VEGF-targeted therapy and nine prior erlotinib. Median number of treatment cycles was 2 (range, 1-7). Common toxicities included rash (72 %), diarrhea (25 %), venous thromboembolic events (15 %), and hypertension (11 %). One patient

demonstrated partial response and seven others stable disease for >2 cycles. CA19-9 decline ≥ 25 percent was observed in 4/26 patients with baseline levels $>2x$ ULN. Estimated median time to progression was 40 days and median survival 102 days (95 % confidence interval 74-117 days), with a 6-month survival rate of 22 percent. Baseline concentration of circulating endothelial cells (CD45(-)/CD34(+)/CD31(+)) was inversely associated with overall survival. It was concluded that the combination of bevacizumab and erlotinib is safe but relatively ineffective in patients with gemcitabine-refractory metastatic pancreatic cancer. Future studies should focus on refining subsets of patients in this challenging population likely to benefit from treatment beyond first-line [732].

Belinostat

A phase I study assessed the maximum tolerated dose, dose-limiting toxicity (DLT) and pharmacokinetics of the histone deacetylase inhibitor belinostat with carboplatin and paclitaxel and the anti-tumour activity of the combination in solid tumours. Cohorts of three to six patients were treated with escalating doses of belinostat administered intravenously once daily, days 1-5 q21 days; on day 3, carboplatin (area under the curve (AUC) 5) and/or paclitaxel (175 mg/m^2) were administered 2-3 h after the end of the belinostat infusion. In all 23 patients received 600-1000 mg/m^2 per day of belinostat with carboplatin and/or paclitaxel. No DLT was observed. The maximal administered dose of belinostat was 1000 mg/m^2 per day for days 1-5, with paclitaxel (175 mg/m^2) and carboplatin AUC 5 administered on day 3. Grade III/IV adverse events were (n; %): leucopenia (5; 22 %), neutropenia (7; 30 %), thrombocytopenia (3; 13 %) anaemia (1; 4 %), peripheral sensory neuropathy (2; 9 %), fatigue (1; 4 %), vomiting (1; 4 %) and myalgia (1; 4 %). The pharmacokinetics of belinostat, paclitaxel and carboplatin were unaltered by the concurrent administration. There were two partial responses (one rectal cancer and one pancreatic cancer). A third patient (mixed mullerian tumour of ovarian origin) showed a complete CA-125 response. In addition, six patients showed a stable disease lasting ≥ 6 months. It was concluded that the combination was well tolerated, with no evidence of pharmacokinetic interaction. Further evaluation of anti-tumour activity is warranted [733].

Bryostatin

To determine the efficacy and toxicity of the protein kinase C inhibitor bryostatin-1 plus paclitaxel in patients with advanced pancreatic carcinoma. Each treatment cycle consisted of paclitaxel 90 mg/m^2 by intravenous infusion over 1 hour on days 1, 8, and 16, plus bryostatin 25 mcg/m^2 as a 1-hour intravenous infusion on days 2, 9, and 15, given every 28 days. Patients were evaluated for response after every 2 treatment cycles, and continued therapy until disease progression or prohibitive toxicity. The primary objective was to determine whether the combination produced a response rate of at least 30 percent. Nineteen patients with locally advanced or metastatic pancreatic adenocarcinoma received a total of 52 cycles of therapy (range: 1-10). Patients received the combination as first-line therapy for advanced disease (n=5) or after prior chemotherapy used alone or in combination with local therapy. No patients had a confirmed objective response. The median time to treatment failure was 2 months (95 % confidence intervals 1 to 3 months). Reasons for discontinuing therapy included progressive disease or death in 14 patients (74 %) or because of adverse events or patient choice in 5 patients (26 %). The most common grade 3 to 4 toxicities included leukopenia in 26 percent, anemia in 11 percent, myalgias in 11 percent, gastrointestinal bleeding in 11 percent, infection in 10 percent, and thrombosis in 10 percent. Thus, the combination of weekly paclitaxel and bryostatin-1 is not an effective therapy for patients with advanced pancreatic carcinoma [734].

Ipilimumab

New, effective therapies are needed for pancreatic ductal adenocarcinoma. Ipilimumab can mediate an immunologic tumor regression in other histologies. This phase II trial evaluated the efficacy of Ipilimumab for advanced pancreatic cancer. Subjects were adults with locally advanced or metastatic pancreas adenocarcinoma with measurable disease, good performance status, and minimal comorbidities. Ipilimumab was administered intravenously (3.0 mg/kg every 3 weeks; 4 doses/course) for a maximum of 2 courses. Response rate by response evaluation criteria in solid tumors criteria and toxicity were measured. Twenty-seven subjects were enrolled (metastatic disease: 20 and locally advanced: 7) with median age of 55 years (27 to 68 y) and good performance status (26 with Eastern Cooperative Oncology Group performance status 0 or 1). Three subjects experienced \geq grade 3 immune-mediated adverse events (colitis 1, encephalitis 1, hypophysitis 1). There were no responders by response evaluation criteria in solid tumors criteria but a subject experienced a delayed response after initial progressive disease. In this subject, new metastases after 2 doses of Ipilimumab established progressive disease. But continued administration of the agent per protocol resulted in significant delayed regression of the primary lesion and 20 hepatic metastases. This was reflected in tumor markers normalization, and clinically significant improvement of performance status. Single agent Ipilimumab at 3.0 mg/kg/dose is ineffective for the treatment of advanced pancreas cancer. However, a significant delayed response in one subject of this trial suggests that immunotherapeutic approaches to pancreas cancer deserve further exploration [735].

Inhibition of renin-angiotensin system

The renin-angiotensin system (RAS) is thought to have a role in carcinogenesis, and RAS inhibition may prevent tumour growth. It was retrospectively investigated the impact of angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) in 155 patients with pancreatic cancer receiving gemcitabine monotherapy. Patients were divided into three groups: the ACEI/ARB group (27 patients receiving an ACEI or ARB for hypertension (HT)), the non-ACEI/ARB with HT group (25 patients receiving antihypertensive drugs other than ACEIs or ARBs), and the non-HT group (103 patients receiving no antihypertensive drugs). Patient characteristics were not different, except for age and HT medications. Progression-free survival (PFS) was 9 months in the ACEI/ARB group, 5 months in the non-ACEI/ARB with HT group, and 4 months in the non-HT group. Overall survival (OS) was 15 months in the ACEI/ARB group, 9 months in the non-ACEI/ARB with HT group, and 10 months in the non-HT group. The use of ACEIs/ARBs was a significant prognostic factor for both PFS and OS in the multivariate analysis. It was concluded that the ACEIs/ARBs in combination with gemcitabine might improve clinical outcomes in patients with advanced pancreatic cancer. Prospective trials are needed to test this hypothesis [736].

Chemoradiotherapy (different cytotoxic drugs)

The optimal management for patients with unresectable locally advanced adenocarcinoma of the pancreas (LAPC) is unclear. The aim of this study was to determine the outcome of patients treated with chemoradiotherapy (CRT) with or without induction chemotherapy. It was conducted a multi-centre retrospective analysis of 48 patients with biopsy-proven LAPC treated with CRT in four regional oncology centres in the UK between 2000 and 2007. The prescribed radiotherapy dose was 4500-5040 cGy in 25-28 fractions and was given concurrent with gemcitabine (n=37), gemcitabine/cisplatin (n=9), 5-fluorouracil (n=1) or capecitabine (n=1). Four patients (8.3%) did not complete the intended treatment due to

CRT-related toxicities. The disease control rate (Objective response rate (ORR) and stable disease (SD)) was 81 percent. The median overall survival was 17 months (range 5-66 months). In subgroup analysis, a trend towards improved survival was seen in patients who completed the intended treatment (17 months vs 11 months) and in patients undergoing surgery (27 months vs 16 months). This is the largest reported series from the UK focussing on patients who received CRT for pancreas cancer. It shows that it is possible to deliver pancreatic CRT with acceptable toxicity. Induction chemotherapy followed by gemcitabine-based CRT shows promising activity and should be evaluated in phase III studies [737].

Image-guided stereotactic radiosurgery

Locally advanced unresectable pancreatic adenocarcinoma is characterized by poor survival despite chemotherapy and conventional radiation therapy (RT). Recent advances in real-time image-guided stereotactic radiosurgery (SRS) have made it possible to treat these cancers in two to four fractions followed by systemic chemotherapy. The aims of one study included to obtain local control of the disease, to improve the survival of these unresectable patients, to evaluate the toxicity of SRS and to report results of the largest series from a single center. Pancreatic SRS involves delivery of high doses of accurately targeted radiation given non-invasively in two to four fractions. It was treated 85 consecutive patients with locally advanced and recurrent pancreatic adenocarcinoma from 2004 to 2009. It was 80 adenocarcinoma, three islet cell, two other. Pre-SRS staging: T(3-4) 85; N(+) 16, N(x) 57, N(0) 12; M(0) 64, M(1) 21. All patients were unresectable at the time of SRS. Seventy-one had no prior surgical resection, and 14 had local recurrence after prior surgical resection. Twenty-nine patients had progression of disease after prior conventional RT. Location of the tumor: head, 57; body and tail, 28. Pre-SRS chemotherapy was given in 48 patients. All patients received gemcitabine-based chemotherapy regimen after SRS. Median tumor volume was 60 cm³. PET/CT scans done in 55 patients were positive in 52 and negative in three patients. Average maximum standard uptake value was 6.9. Pain score on a scale of 1-10 was: 0-3 in 54, 4-7 in 18, and 8-10 in 13 patients. SRS doses ranged from 15 to 30 Gy with a mean dose of 26 Gy delivered in 3 days divided in equal fractions. Mean conformality index was 1.6, and mean isodose line was 80 percent. Complete, partial, and stable disease were observed in 78 patients for the duration of 3-36 months with median of 8 months. Pain relief was noted in majority of patients lasting for 18-24 weeks. Most of the patients died of distant disease progression while their primary tumor was controlled. Overall median survival from diagnosis was 19 months and from SRS it was 9 months. For the group of 35 patients with adenocarcinoma without prior surgical resection or RT and no distant metastases, the average and 1-year survival from diagnosis was 15 months and 50 percent, respectively, and from SRS it was 11 months and 31 percent, respectively. A total of 19 (22 %) patients developed grades III/IV GI toxicity including duodenitis, 12 (14 %); gastritis, 11 (13 %); diarrhea, three (4 %); and renal failure was noted in one (1 %). Three patients had both gastritis and duodenitis. Toxicity was significantly more prevalent in the first 40 patients compared with the last 45 patients (33 vs 14 %). It was concluded that SRS for unresectable pancreatic carcinoma can be delivered in three fractions with minimal morbidity and a local tumor control rate of 92 percent. The survival is comparable or better than the reported results for advanced pancreatic cancer, specifically for the group of previously untreated patients with unresectable tumors. Development of distant metastases remains a significant factor [738].

CybeKnife® is a newly developed technology in the field of stereotactic radiosurgery/radiotherapy (SRS/SRT). Compared with conventional SRS/SRT, there are many advantages for CyberKnife in terms of treating tumors that move with respiration, being real-time image-guidance, frameless, high accurateness, and so on. Recently, it has been used to treat different types of malignant carcinoma including intracranial and caudomedial tumors. One study was designed to evaluate the short-term efficacy and toxicity of the CyberKnife

radiotherapy for locally advanced pancreatic cancer. A total of 20 patients with locally advanced (stage II-III) pancreatic cancer treated with CyberKnife were recruited in 2009. Of 20 patients, 13 were with cancer located at the pancreatic head and 7 were located at the pancreatic body and tail. The planning target volume (PTV) was defined as gross tumor volume (GTV) plus 2-3 mm, and more than 95 percent PTV should be covered by 75 percent isodose surface. The median of PTV was 47 cm³ (26-64 cm³). The median total prescription dose was 40 Gy (32-55 Gy) at 3-6 fractions. During treatment delivery, X-Sight Spine Tracking System was used in 5 patients to track movement of the tumor. Another 15 patients were implanted fiducials in the tumors to track movement of the tumor and patient breathing patterns. The median follow-up time was 7 months (3-11 months). All patients had finished the treatment and 19 were alive by the last follow-up. Slight fatigue was the most common complain. Evaluated by CT scan, 6 were complete response, 9 were partial response, 3 were stable disease, and 1 was progression; 1 was dead. There were 6 patients with grade I granulocytopenia, 7 with grade I nausea, and 5 with grade II vomiting. The authors concluded that CyberKnife radiosurgery for the locally advanced pancreatic cancer shows a high rate of local control and minimal toxicity, but long-term follow-up is necessary to evaluate the survival and late toxicity [739].

Chemoradiation in elderly

To review the outcomes and tolerability of full-dose chemoradiation in elderly patients aged 75 years or older with localized pancreatic cancer it was retrospectively reviewed patients aged 75 years or older with nonmetastatic pancreatic cancer treated with chemoradiation therapy at two institutions from 2002 to 2007. Patients were analyzed for treatment toxicity, local recurrences, distant metastases, and survival. A total of 42 patients with a median age of 78 years (range, 75-90 years) who received chemoradiation therapy for pancreatic cancer were identified. Of the patients, 24 had locally advanced disease treated with definitive chemoradiation, and 18 had disease treated with surgery and chemoradiation. Before chemoradiotherapy, the mean Eastern Cooperative Oncology Group performance status was 1.0 ± 0.8, and the mean 6-month weight loss was 5.3 ± 3.8 kg. The mean radiation dose delivered was 48.1 ± 9.2 Gy. All patients received fluoropyrimidine-based chemotherapy concurrently with radiotherapy. In all, 8 patients (19 %) were hospitalized, 7 (17 %) had an emergency room visit, 15 (36 %) required a radiation treatment break, 3 (7 %) required a chemotherapy break, 9 (21 %) did not complete therapy, and 22 (49 %) had at least one of these adverse events. The most common toxicities were nausea, pain, and failure to thrive. Median overall survival was 9 months (95 % confidence interval 7 to 13 months) in patients who received definitive chemoradiation therapy and 21 months (95 % confidence interval 10 to infinity) in patients who underwent resection and chemoradiation therapy. The authors concluded that in this dataset of very elderly patients with pancreatic cancer and good Eastern Cooperative Oncology Group performance status, outcomes after chemoradiotherapy were similar to those among historic controls for patients with locally advanced and resected pancreatic cancer, although many patients experienced substantial treatment-related toxicity [740].

External radiotherapy

To analyze retrospectively the results of postoperative external beam radiotherapy (EBRT) for resected pancreatic adenocarcinoma the records of 47 patients treated with gross complete resection (R0: 24 patients, R1: 23 patients) and post-operative EBRT were reviewed. The median dose of EBRT was 50 Gy (range, 12-60 Gy), and chemotherapy was used in 37 patients (79 %). The median follow-up period for all 47 patients was 14 months (range, 1-68 months). At the time of this analysis, 24 patients (51 %) had disease recurrence.

Local failure was observed in 10 patients (21 %), and the 2-year local control (LC) rate in all patients was 69 percent. Patients treated with EBRT and chemotherapy had a significantly more favorable LC (2-year LC rate: 76 %) than those treated with EBRT alone (2-year LC rate: 40 %). The median survival time and the 2-year actuarial overall survival (OS) in all 47 patients were 30 months and 55 percent, respectively. Patients treated with EBRT and chemotherapy had a significantly more favorable OS (2-year OS rate: 62 %) than those treated with EBRT alone (2-year OS: 25 %). On univariate analysis, chemotherapy use alone had a significant impact on OS, and on multivariate analysis, chemotherapy use also was a significant prognostic factor. There were no late morbidities of NCI-CTC Grade 3 or greater. It was concluded that post-operative EBRT with chemotherapy yields a favorable LC rate for resected pancreatic adenocarcinoma, and EBRT combined with chemotherapy confers a survival benefit compared to EBRT alone [741].

Pattern of use in Japan

A questionnaire-based national survey of radiotherapy for pancreatic cancer treated between 2000 and 2006 was conducted by the Japanese Radiation Oncology Study Group (JROSG). Detailed information on 870 patients from 34 radiation oncology institutions was accumulated. The median age of all patients was 64 years (range, 36-88), and 80 percent of the patients had good performance status. More than 85 percent of patients had clinical Stage T3-T4 disease, and 69 percent of patients had unresectable disease at diagnosis. Concerning radiotherapy (RT), 50 percent of patients were treated with radical external beam radiotherapy (EBRT) (median dose, 50.4 Gy), 44 percent of patients were treated with intraoperative radiotherapy (median dose, 25 Gy) with or without EBRT (median dose, 45 Gy), and 6 percent of patients were treated with postoperative radiotherapy (median dose, 50 Gy). The treatment field consisted of the primary tumor (bed) only in 56 percent of the patients. Computed tomography-based treatment planning and conformal RT was used in 93 percent and 83 percent of the patients treated with EBRT, respectively. Chemotherapy was used for 691 patients (79 %; before radiotherapy for 66 patients; during radiotherapy for 531; and after radiotherapy for 364). Gemcitabine was the most frequently used drug, followed by 5-fluorouracil [742].

Dose escalation for pancreas cancer is limited by the tolerance of adjacent normal tissues, especially with stereotactic body radiotherapy (SBRT). The duodenum is generally considered to be the organ at greatest risk. This study reports on the dosimetric determinants of duodenal toxicity with single-fraction SBRT. Seventy-three patients with locally advanced unresectable pancreatic adenocarcinoma received 25 Gy in a single fraction. Dose-volume histogram (DVH) endpoints evaluated include V (5) (volume of duodenum that received 5 Gy), V(10), V(15), V(20), V(25), and D(max) (maximum dose to 1 cm³). Normal tissue complication probability (NTCP) was evaluated with a Lyman model. Univariate and multivariate analyses were conducted with Kaplan-Meier and Cox regression models. The median time to Grade 2-4 duodenal toxicity was 6 months (range, 2-12 months). The 6- and 12-month actuarial rates of toxicity were 11 percent and 29 percent, respectively. V(10)-V(25) and D(max) all correlated significantly with duodenal toxicity. In particular, V(15) \geq 9.1 cm³ and V(15) < 9.1 cm³ yielded duodenal toxicity rates of 52 percent and 11 percent, respectively; V(20) \geq 3.3 cm³ and V(20) < 3.3 cm³ gave toxicity rates of 52 percent and 11 percent, respectively; and D(max) \geq 23 Gy and D(max) < 23 Gy gave toxicity rates of 49 percent and 12 percent, respectively. Only the Lyman NTCP model remained significant in multivariate analysis. It was concluded that multiple DVH endpoints and a Lyman NTCP model are strongly predictive of duodenal toxicity after SBRT for pancreatic cancer. These dose constraints will be valuable in future abdominal stereotactic body radiotherapy studies [743].

Radiotherapy planning

Intensity-modulated radiotherapy (IMRT) allows for improved sparing of organs at risk (OARs) in advanced pancreatic cancer. A planning study evaluated if volumetric modulated arc therapy (RapidArc [RA]) could be used as an alternative to IMRT in such cases. In ten patients, five-field IMRT (5f-IMRT) plans with fixed gantry positions were compared to RA plans using similar constraints for planning target volume (PTV) and OARs. PTV coverage, conformity indices (CI), and OAR doses were compared. One patient was treated using RA and calculated dose distributions were measured in coronal planes in a solid-water phantom. It was concluded that RA planning achieved superior CI for pancreatic tumors compared to 5f-IMRT, and modestly reduced OAR doses. Fast treatment delivery using RA may decrease the risk of intrafractional organ motion [744].

Radiofrequency ablation

Radiofrequency ablation (RFA) is a local ablative method used for the palliative treatment of solid tumors, and it should be an attractive approach in patients with unresectable, locally advanced, and nonmetastatic pancreatic cancer. It was aimed to systematically review the results of RFA in pancreatic adenocarcinoma on the basis of recent literature to evaluate the clinical benefit of this technique. For this purpose, a search was made on February 26, 2010 using the MEDLINE/PubMed database to select the data existing in the literature on ductal pancreatic adenocarcinoma treated with RFA. It was identified 7 papers useful for this systematic review. The 7 manuscripts reported data of 106 patients (47 women, 59 men; mean age 65 years). The tumor was localized in the head of the pancreas in 71 patients (67 %) and in the body-tail in 35 (33 %); the size of the tumor was 4.6 cm. Eighty-five patients (80 %) had a locally advanced cancer, and 21 patients (20 %) had a metastatic disease. Almost all the procedures were performed during laparotomy (105/106); only one thermoablation was computed tomography guided for a pancreatic cancer located in the body of the pancreas. Other palliative surgical procedures were carried out in only 44 patients: 32 double bypasses (common bile duct-jejunostomy plus gastrojejunostomy, 67 %), 8 gastric bypasses (17 %), 4 cholecystojejunostomies (8 %), 3 common bile duct-jejunostomies (6 %), and 1 pancreaticojejunostomy (2 %). The ratio between the number of passes of the probe and the size of the tumor was calculated in only 17 procedures owing to the lack of data. Data regarding the thermal kinetic characteristics were available in 5 studies for a total of 99 patients. The median temperature used was 90°C (range, 30-105). The median time of duration for each application of the probe in 49 patients in whom this parameter was reported was 11 minutes. Regarding postoperative outcome, data were available in all the studies; the median postoperative morbidity rate was 28 percent (30/106 patients), and a total of 35 complications were present in the 30 patients: 8, gastrointestinal hemorrhage; 5, pancreatic fistula; 5, biliary leak; 4, portal vein thrombosis; 3, pseudocyst; 2, sepsis; 1, polyuria; 1, ascites; 1, pneumonia; 1, liver failure; 1, anastomotic ulcer; 1, severe acute pancreatitis; 1, renal failure; and 1, delayed gastric emptying. The rate of repeated laparotomy was 3.7 percent, and the mortality rate was 7.5 percent. The median survival was 5 months (range, 1-33 months) calculated on 40 patients in whom this information was available. The critical points of the studies on RFA are that all of them were retrospective, and there were no randomized studies; there were also large differences in the selection of patients undergoing RFA in surgical skill. Furthermore, RFA may cause inadvertent thermal necrosis of the intrapancreatic common bile duct or duodenum, and for this reason, some authors routinely performed a double surgical bypass in the lesions of the head. However, the complication rate seems high without a clear benefit of survival. Therefore, the RFA procedure is not recommended as palliative therapy in clinical practice for patients with unresectable pancreatic adenocarcinoma [745].

Vaccines

Mucin 1 (MUC1), a bound mucin glycoprotein, is overexpressed and aberrantly glycosylated in >80 percent of human ductal pancreatic carcinoma. Evidence suggests that MUC1 can be used as a tumor marker and is a potential target for immunotherapy of pancreatic cancer. However, vaccination with MUC1 peptides fails to stimulate the immune response against cancer cells because immunity toward tumor-associated antigens (TAA), including MUC1, in cancer patients is relatively weak, and the presentation of these TAAs to the immune system is poor due to their low immunogenicity. It was investigated whether vaccination with immunogenetically enhanced MUC1 (by expressing alpha-gal epitopes; Galalpha1-3Galbeta1-4GlcNAc-R) can elicit effective antibody production for MUC1 itself as well as certain TAAs derived from pancreatic cancer cells and induced tumor-specific T-cell responses. It was also used alpha1,3galactosyltransferase (alpha1,3GT) knockout mice that were preimmunized with pig kidney and transplanted with B16F10 melanoma cells transfected with MUC1 expression vector. Vaccination of these mice with alpha-gal MUC1 resulted in marked inhibition of tumor growth and significant improvement of overall survival time compared with mice vaccinated with MUC1 alone. Furthermore, vaccination with pancreatic cancer cells expressing alpha-gal epitopes induced immune responses against not only differentiated cancer cells but also cancer stem cells. The results suggested that vaccination using cells engineered to express alpha-gal epitopes is a novel strategy for treatment of pancreatic cancer [746].

Personalized peptide vaccination combined with gemcitabine

It was evaluated the safety of, and clinical and immune responses to personalized peptide vaccination with gemcitabine (GEM) as the first line therapy in patients with non-resectable pancreatic cancer. Pre-vaccination peripheral blood mononuclear cells (PBMCs) and plasma were prepared to examine cellular and humoral responses to 14 and 16 peptides in human leukocyte antigen (HLA)-A24+ or -A2+ patients, respectively. Only the reactive peptides (maximum of 4) were administered weekly at 3 mg/peptide. GEM was administered at 1000 mg/m² per week for 3 weeks, followed by 1 week of rest. Twenty-one patients with untreated and non-resectable pancreatic cancer were enrolled. The combination therapy was generally well tolerated. Boosting of cellular and humoral responses to the vaccinated peptides was observed in the post-vaccination (eighth) PBMCs and plasma from 14 of 18 and 13 of 18 patients tested, respectively. The best clinical responses were 7 cases of partial response, 9 cases of stable disease, and 5 cases of progressive disease. Median survival time of all 21 patients was 9 months (95 % confidence interval 6-16 months) with a one year survival rate of 38 percent. Immune boosting in both cellular and humoral responses was well correlated with overall survival with a hazard ratio of 0.2 (95 % confidence interval 0.06 to 0.73) The results suggest a potential clinical benefit of this combination therapy for non-resectable pancreatic cancer patients as the first line therapy. Further exploration of this approach is warranted [747].

New therapeutic options

Pancreatic cancer (PC) is a highly lethal disease with complex etiology involving both environmental and genetic factors. Although cigarette smoking is known to explain 25 percent of cases, data from recent studies suggest that obesity and long-term type II diabetes are two major modifiable risk factors for PC. Furthermore, obesity and diabetes seem to affect the clinical outcome of patients with PC. Understanding the mechanistic effects of obesity and diabetes on the pancreas may identify new strategies for prevention or therapy. Experimental and epidemiologic evidence suggests that the antidiabetic drug metformin has protective antitumor activity in PC. In addition to insulin resistance and

inflammation as mechanisms of carcinogenesis, obesity and diabetes are linked to impairments in endothelial function and coagulation status, which increase the risks of thrombosis and angiogenesis and, in turn, the risk of PC development and progression. The associations of the ABO blood group gene and NR5A2 gene variants with PC discovered by recent genome-wide association studies may link insulin resistance, inflammation, and thrombosis to pancreatic carcinogenesis. These exciting findings open new avenues for understanding the etiology of PC and provide opportunities for developing novel strategies for prevention and treatment of this disease [748].

High-intensity focused ultrasound ablation

The aim of one study was to evaluate the safety and efficacy of ultrasound-guided high-intensity focused ultrasound therapeutic ablation of solid tumors in difficult locations. A procedure was performed with a focused ultrasound tumor therapeutic system which provides real-time ultrasound guidance. All patients underwent MDCT or MRI, and some patients underwent PET/CT. From 2007 through 2009, 31 patients with 38 lesions of the liver and pancreas in difficult locations were treated. Six patients had hepatocellular carcinoma, 13 patients had hepatic metastasis from colorectal cancer, two had hepatic metastases of breast cancer, two had hepatic metastasis of neuroendocrine tumors, one patient had lymph node metastasis of breast cancer at the hepatic hilum, six patients had pancreatic cancer, and one patient had a neuroendocrine tumor. Difficult location was defined as tumor adjacent to a main blood vessel, the heart, the gallbladder and bile ducts, the bowel, or the stomach. The mean diameter of tumors was 2.7 ± 1.4 cm. PET/CT, MDCT, or both on the day after one session of high-intensity focused ultrasound treatment showed complete response in all six patients with hepatocellular carcinoma, the patient with lymph node metastasis, and 22 of 24 patients with hepatic metastasis. The symptoms of all seven patients with pancreatic cancer or neuroendocrine tumors were palliated, and PET/CT or MRI showed complete response of six of seven lesions. Portal vein thrombosis occurred after high-intensity focused ultrasound ablation in one patient with pancreatic cancer. No other side effects were detected in a median follow-up period of 12 months. According to the short- and long-term follow-up results, ultrasound-guided high-intensity focused ultrasound ablation can be considered a safe and feasible approach to the management of solid tumors in difficult locations [749].

Curcumin

Curcumin (diferuloylmethane), a derivative of turmeric is one of the most commonly used and highly researched phytochemicals. Abundant sources provide interesting insights into the multiple mechanisms by which curcumin may mediate chemotherapy and chemopreventive effects on cancer. The pleiotropic role of this dietary compound includes the inhibition of several cell signaling pathways at multiple levels, such as transcription factors (NF- κ B and AP-1), enzymes (COX-2, MMPs), cell cycle arrest (cyclin D1), proliferation (EGFR and Akt), survival pathways (β -catenin and adhesion molecules), and TNF. Curcumin up-regulates caspase family proteins and down-regulates anti-apoptotic genes (Bcl-2 and Bcl-X(L)). In addition, cDNA microarrays analysis adds a new dimension for molecular responses of cancer cells to curcumin at the genomic level. Although, curcumin's poor absorption and low systemic bioavailability limits the access of adequate concentrations for pharmacological effects in certain tissues, active levels in the gastrointestinal tract have been found in animal and human pharmacokinetic studies. Currently, sufficient data has been shown to advocate phase II and phase III clinical trials of curcumin for a variety of cancer conditions including multiple myeloma, pancreatic, and colon cancer [750].

Genistein

Oxaliplatin (OxP) has been used in combination therapy with gemcitabine for the treatment of pancreatic cancer (PC) but the beneficial effect was marginal, which is believed to be due to de novo and acquired drug-resistance of PC. It was reported in vitro and in vivo preclinical evidence in support of chemo-sensitization of drug-resistant cells by a non-toxic chemopreventive agent (genistein). Genistein pretreatment together with low concentration of OxP showed significant reduction in cell viability and colony formation concomitant with increased apoptosis, which was highly synergistic. Drug-resistance of PC is allegedly linked with both constitutive and OxP-induced activation of NF-kappaB, and it was found that inactivation of NF-kappaB by genistein prior to treatment of cells with OxP was required for cell killing, which was consistent with the down-regulation of NF-kappaB and its downstream anti-apoptotic genes (Bcl-2 XIAP's, survivin). Most importantly, the in vivo experiments using orthotopic mouse model showed significant reduction in tumor size and reduction of locoregional lymph node metastasis by combination treatment. These results were also consistent with inactivation of NF-kappaB and the down-regulation of NF-kappaB downstream genes, decreased proliferation marker (Ki-67), and increased apoptosis (TUNEL) in tumor remnants, all of which was consistent with in vitro findings. From these results, it was concluded that genistein sensitizes drug-resistant PC to OxP, which is mechanistically linked with inactivation of NF-kappaB signaling, resulting in greater anti-tumor effects [751].

Immunotherapy

CD40 is a costimulatory molecule widely expressed by immune cells and by neoplastic cells of different histotypes. Engagement of surface CD40 mediates different effects depending on cell type and microenvironment. In particular, CD40 expression on immune cells regulates humoral and cellular immunity, while it has apoptotic and antiproliferative activity on selected neoplastic cells. Thus, CD40 targeting may indirectly affect tumor growth through the activation of immune cells and/or directly by mediating cytotoxic effects on neoplastic cells. Preliminary findings emerging from clinical trials indicate that antibodies to CD40 can induce immune modulation and clinical responses in cancer patients [752].

Lovastatin

In tumor cell masses, the extracellular pH decreases below 6.5. The effect of external acidic pH on the efficacy of 24 chemical compounds including molecular-targeted inhibitors and anti-tumor reagents was investigated in human cancer cells. Lovastatin showed no cytotoxicity in mesothelioma or pancreatic carcinoma cells at concentrations up to 10 μ M and pH around 7.4, but 10 μ M lovastatin decreased the survival of these cells below 40 percent at acidic pH. Lovastatin inhibits HMG-CoA reductase, resulting in a decrease in the levels of cholesterol and prenylated proteins. An inhibitor of the former pathway showed pH-independent cytotoxic activity, whereas an inhibitor of the latter pathway had stronger activity at acidic pH. The inhibitory efficacy of cantharidin also increased at acidic pH. On the other hand, no pH dependency or slightly impaired efficacy at low pH conditions was observed in other 20 reagents, and especially, the activity of aphidicolin was suppressed under acidic conditions. These results suggested that screening under acidic conditions would be useful for developing new chemotherapeutic reagents [753].

Apoptotic aspects

Pancreatic cancer cells are highly resistant to drug therapy; however, underlying causes remain largely unknown. It was hypothesized that the activation of CXCL12-CXCR4 signalling confers drug resistance to pancreatic cancer cells by potentiating survival. CXCR4

is overexpressed in precancerous/malignant pancreatic lesions and cancer stem cells, and implicated in its pathogenesis. Effect of CXCR4 activation by CXCL12 on restricting the gemcitabine-induced cytotoxicity and stimulating the survival signalling was examined in pancreatic cancer cells by MTT, DNA laddering, caspase activity, immunoblot, and promoter-reporter assays. Subsequently, we examined the effect of CXCR4 antagonist, AMD3100, in abrogating the rescue effect of activated CXCL12-CXCR4 signalling. The pancreatic cancer cells treated with gemcitabine exhibited reduced cytotoxicity in the presence of CXCL12 as compared with the cells treated with drug alone. CXCL12 induced the activation of FAK, ERK, and Akt signalling pathways, enhanced transcriptional activities of β -catenin and NF- κ B, and expression of survival proteins. AMD3100 arrested the CXCL12-induced pancreatic cancer cell growth and drug resistance. The findings demonstrate, for the first time, a role of CXCL12-CXCR4 signalling axis in conferring drug resistance to pancreatic cancer cells and suggest that it could serve as a novel therapeutic target for pancreatic cancer therapy, alone and in combination with the cytotoxic drug [754].

Etoposide particles

Amphiphilic diblock copolymers composed of methoxy poly ethylene glycol (MePEG) and poly epsilon caprolactone (PCL) were synthesized for the formation of micelles by ring opening mechanism using stannous octoate as a catalyst. The effects of the molecular weight of MePEG and the copolymer ratio on the properties of micelles were investigated by Nuclear Magnetic Resonance (1 H-NMR), Fourier Transform Infrared Spectroscopy (FT-IR), and Gel Permeation Chromatography (GPC). The diblock copolymers were self-assembled to form micelles and their hydrophobic core was used for the encapsulation of the anti-cancer drug (etoposide) in aqueous solution. The sizes of micelles were less than 250 nm with a narrow size distribution with monodispersed unimodal pattern. Differential Scanning Calorimetric (DSC) thermogram was done for etoposide-loaded micelles to understand the crystalline nature of the drug after entrapment. A drug loading capacity up to 60 percent (w/w) with an entrapment efficiency of 68% was achieved as determined by reverse phase high performance liquid chromatography (RP-HPLC). In vitro release kinetics showed a biphasic release pattern of etoposide for 2 weeks. The cytotoxic efficacy of the etoposide-loaded micelles demonstrated greater anti-proliferative activity (IC_{50} =1.1 microg/mL) as compared to native drug (IC_{50} =6.3 microg/mL) in pancreatic cancer cell line MIA-PaCa-2. Thus, etoposide-loaded MePEG/PCL block copolymeric micelles can be used as an efficient drug delivery vehicle for pancreatic cancer therapy [755].

Interferons

Clinical trials on pancreatic cancer demonstrated that interferons (IFN) improve the therapeutic index of combined radio- and chemotherapy. This is believed to be due to radiosensitisation of cells, which, however, needs experimental verification. It was therefore compared the survival response of ten pancreatic tumour cell lines following ionising radiation (IR), interferon-alpha (IFN-alpha), interferon-beta (IFN-beta) and combined treatment. The effect of combination treatment on apoptosis induction was also determined. In most cell lines IFN treatment on its own exerted cytotoxicity, which was independent of the expression level of the IFN receptor on the cell surface. Three cell lines showed a radiosensitisation effect while two showed radioprotection. Although IFN-alpha is commonly used in the clinic, IFN-beta induced a stronger cytotoxic response than IFN-alpha in vitro. The likely mechanism of enhancement of radiosensitivity in the responsive cell lines was shown to be an increase of the radiation-induced apoptotic response by IFN pretreatment. Given that the in vitro data do not conform to the impressive clinical results observed after combined radio- and chemotherapy with IFN-alpha, it is reasonable to conclude that the sensitising effect of IFN is not mediated through modulating the intrinsic radiosensitivity of pancreatic cancer cells [756].

Nanoparticles with cetuximab

Gold and carbon nanoparticles absorb nonionizing radio frequency (RF) energy and release heat. Solid gold nanoparticles are delivered to cancer cells via conjugation with targeting antibodies. Here, 20-nm gold particles were conjugated to cetuximab, which is an epidermal growth factor receptor-1 (EGFR-1) antibody. A pancreatic carcinoma cell line that highly expresses EGFR-1, Panc-1, and Cama-1, which is a breast carcinoma cell line that minimally expresses EGFR-1, were treated with 100-nmol/L cetuximab-conjugated gold nanoparticles for 3 h (n=4). Thirty-six hours later, the dishes were placed in an RF field with a generator power of 200 W for 5 min. After another 36 h, cell injury and death were evaluated with flow cytometry. The targeted cell line Panc-1 had a viability of $46 \% \pm 12 \%$, whereas the Cama-1 cell had a viability of $92 \% \pm 2 \%$ after RF field exposure, which was a significant difference. Transmission electron microscopy showed gold nanoparticle uptake in Panc-1 cells but negligible uptake by Cama-1 cells. Nontargeted cells do not internalize a sufficient amount of antibody-conjugated gold nanoparticles to induce injury in a noninvasive RF field. It was concluded that this technique could be useful in cancer treatment if a cancer-specific antibody is used to localize gold nanoparticles to malignant cells [757].

“Alternative” therapies

Conventional medicine has had little to offer patients with inoperable pancreatic adenocarcinoma; thus, many patients seek alternative treatments. The National Cancer Institute, in 1998, sponsored a randomized, phase III, controlled trial of proteolytic enzyme therapy versus chemotherapy. Because most eligible patients refused random assignment, the trial was changed in 2001 to a controlled, observational study. All patients were seen by one of the investigators, and patients who received enzyme therapy were seen by the participating alternative practitioner. Of 55 patients who had inoperable pancreatic cancer, 23 elected gemcitabine-based chemotherapy, and 32 elected enzyme treatment, which included pancreatic enzymes, nutritional supplements, detoxification, and an organic diet. Primary and secondary outcomes were overall survival and quality of life, respectively. At enrollment, the treatment groups had no statistically significant differences in patient characteristics, pathology, quality of life, or clinically meaningful laboratory values. Kaplan-Meier analysis found a 10-month difference in median survival between the chemotherapy group (median survival, 14 months) and enzyme treatment groups (median survival, 4 months) and found an adjusted-mortality hazard ratio of the enzyme group compared with the chemotherapy group of 7.0. At 1 year, 56 percent of chemotherapy-group patients were alive, and 16 percent of enzyme-therapy patients were alive. The quality of life ratings were significantly better in the chemotherapy group than in the enzyme-treated group [758].

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Intraductal papillary mucinous neoplasms (IPMNs), characterized by intraductal papillary growth and thick mucin secretion, have increasingly been recognized. Despite modern preoperative evaluation, major difficulties still remain in distinguishing malignant invasive types from benign IPMNs. Following a PubMed database search, all relevant abstracts and articles on IPMN published in English and Chinese were reviewed. Main-duct and the mixed type IPMNs carry a higher risk of malignancy as compared with branch-duct type IPMNs. Treatment of branch-duct type IPMNs remains controversial. Once operation is indicated, intraoperative frozen section of margins plays an important role in the decision concerning the extent and type of surgery. Pancreatectomy, partly preserving both endocrine and exocrine pancreatic function, is advocated for most patients with IPMN, though total pancreatectomy may be necessary in some. Both for patients subjected to surgery and those only observed, IPMN patients need regular close follow-up to identify recurrence or progressive disease [759].

Intraductal papillary mucinous neoplasms (IPMN) are mucinous cystic tumors of the pancreas, which were first classified into a unified diagnosis by the World Health Organization in 1996. These lesions originate from the cells of the pancreatic ductal system and may grossly or microscopically involve the pancreatic ducts in a diffuse or multifocal fashion. As experience with IPMN increases, it is becoming more evident that this process presents as a spectrum of neoplasia with significant variation regarding the clinical and radiologic presentation, malignant potential, and disease-specific outcome. IPMN encompasses a spectrum of precursor lesions, from adenoma to intraductal carcinoma to invasive cancer, with molecular data supporting the premise that this dysplastic process has the potential to progress from low-grade dysplasia to invasive carcinoma. Controversy over the management of IPMN exists because of the difficulty in obtaining a preoperative histologic diagnosis, the broad spectrum of neoplasia, the lack of understanding as to the frequency and time to malignant progression [760].

Intraductal papillary mucinous neoplasm (IPMN) is an intraductal mucin-producing epithelial neoplasm that arises from the main pancreatic duct (MD-IPMN), secondary branch ducts (BD-IPMN), or both (mixed type; Mix-IPMN). Neoplastic progression from benign adenoma to invasive adenocarcinoma has not been proven but is generally thought to occur. With increasing recognition of IPMN, our understanding of the diagnosis and management of the tumors is evolving. At present, treatment options for patients with IPMN range from observation to pancreatic resection depending on the natural history of the lesion [761].

Classification

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is divided into 4 subtypes: an intestinal type, a gastric type, a pancreatobiliary type, and an oncocytic type. The purposes of one study were to clarify the outcomes and the characteristics of invasive carcinoma derived from IPMN (invasive IPMC) by focusing on these subtypes with a comparison to conventional invasive ductal carcinoma (IDC) of the pancreas. A total of 30 patients with invasive IPMC were reviewed, and the tumors were divided into 2 pathologic subtypes, intestinal and nonintestinal type. The prognosis and characteristics of the 2 subtypes were evaluated. Furthermore, the prognosis of 119 patients with conventional IDC was compared with that of patients with invasive carcinoma derived from the intestinal or nonintestinal type IPMN. The 5-year survival rate of patients with the nonintestinal type (0 %) was as poor as that of patients with conventional IDC (20 %). The patients with the intestinal type (67 %) had a more favorable prognosis than patients with conventional IDC. The

nonintestinal type was characterized by positive lymphatic invasion and tubular invasive pattern. It was concluded that invasive carcinoma derived from the nonintestinal type IPMN characterized by lymphatic invasion and tubular invasive pattern is associated with a poor prognosis [762].

Molecular biology

Molecular overview

Over the last 3 decades, there have been substantial improvements in diagnostic imaging and sampling techniques to evaluate pancreatic diseases. The modern technology has helped us to recognize premalignant conditions of pancreas including mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs). Differentiation between benign and malignant lesions and early detection of any malignant transformation in premalignant lesion are extremely important for further management decisions. Diagnostic cytology has limited sensitivity to further differentiate between benign, premalignant, and malignant lesions of the pancreas. There is limited information about the epidemiological risk factors and molecular mechanisms leading to development and further progression to malignancy of IPMNs. Several studies have shown that pancreatic juice and pancreatic tissue from the lesion can be tested for molecular markers including K-ras, p53, and p16 to differentiate between cancer and chronic inflammatory process. It was reviewed cellular signaling pathways that contribute to pathogenesis of IPMNs of the pancreas to further identify potential biomarkers and molecular targets [763].

Apoptosis

Intraductal papillary mucinous neoplasm is characterized by cystically dilated main and/or branch pancreatic duct with mucus. According to the degree of atypia, intraductal papillary mucinous neoplasm is classified into 3 groups: adenoma, borderline, and carcinoma. Furthermore, intraductal papillary mucinous neoplasm is considered to progress through an adenoma-carcinoma sequence like colorectal carcinoma. Programmed cell death 4 is a recently identified tumor suppressor that was found to inhibit translation. Programmed cell death 4 has been reported to inhibit tumorigenesis, tumor progression, proliferation, invasion, and metastasis in several human malignancies. It was examined 108 cases of intraductal papillary mucinous neoplasm by immunohistochemistry and revealed that programmed cell death 4 expression was recognized in both the nucleus and cytoplasm in intraductal papillary mucinous neoplasm. The positive rate of programmed cell death 4 was 79 percent, 43 percent and 10 percent in adenoma, borderline, and carcinoma, respectively. The positive rate of programmed cell death 4 significantly decreased from adenoma to carcinoma, indicating that programmed cell death 4 might inhibit tumor progression in intraductal papillary mucinous neoplasm. Programmed cell death 4 expression had a strong relationship with p21 expression and an inverse correlation with Ki-67 labeling index. Thus, programmed cell death 4 might inhibit the proliferation of intraductal papillary mucinous neoplasm; and its inhibition might partly result from cell cycle arrest caused by the up-regulation of p21. In conclusion, programmed cell death 4 may inhibit tumor progression in intraductal papillary mucinous neoplasm; and the loss of programmed cell death 4 expression is representative of the malignant potential of intraductal papillary mucinous neoplasm including the proliferative activity. Therefore, programmed cell death 4 can be an important biomarker for intraductal papillary mucinous neoplasm [764].

CD24

CD24 is a molecule involved in cell adhesion and tumor metastasis. The aims of this study were to evaluate the association between CD24 expression and the progression of intraductal papillary mucinous neoplasms of the pancreas and to investigate the association between CD24 expression in pancreatic cancer and the prognosis of patients who underwent curative pancreatectomy. Immunohistochemical analysis of CD24 was performed for 95 intraductal papillary mucinous neoplasms of the pancreas and 83 pancreatic cancers. We investigated the association between CD24 expression and the histologic grade of intraductal papillary mucinous neoplasms of the pancreas, the clinicopathologic parameters of pancreatic cancers, and the survival time of pancreatic cancer patients who underwent pancreatectomy. The positive rates of CD24 expression in intraductal papillary mucinous adenoma, borderline intraductal papillary mucinous neoplasm, noninvasive intraductal papillary mucinous carcinoma, and invasive intraductal papillary mucinous carcinoma were 5 (20 %) of 24, 12 (48 %) of 25, 10 (43 %) of 23, and 15 (65 %) of 23, respectively. The CD24-positive rates were significantly higher in borderline intraductal papillary mucinous neoplasm and intraductal papillary mucinous carcinoma compared with intraductal papillary mucinous adenoma. The staining scores, which were determined from the percentage of stained cells and the staining intensity, were significantly higher in invasive intraductal papillary mucinous carcinoma than in noninvasive intraductal papillary mucinous carcinoma. In the pancreatic cancers, higher tumor stage, nodal metastasis, and higher-grade tumors were more frequent in the CD24-positive group compared with the CD24-negative group. CD24 expression was associated with shorter survival in univariate analysis. However, based on the multivariate analysis, the CD24 expression was not associated with survival. In conclusion, CD24 is involved in the progression of intraductal papillary mucinous neoplasms of the pancreas and in the malignant behavior of pancreatic cancers [765].

CD44v6

The purpose of one study was to examine CD44v6 expression in intraductal papillary mucinous neoplasms (IPMNs) and clarify the role of CD44v6 in progression, invasion, metastasis, and morphogenesis of IPMNs. One hundred fifty-one samples of IPMNs and 30 normal controls were subjected to immunohistochemical analysis for CD44v6. The IPMNs were divided into 4 groups according to the grade of atypia (adenoma, borderline IPMN, noninvasive carcinoma, and invasive carcinoma) and 5 subtypes according to histological phenotype (gastric, intestinal, pancreatobiliary, oncocytic, and unclassified). Correlations were investigated between CD44v6 expression and clinicopathological characteristics including grade of atypia, subtype, lymph node metastasis, and invasion pattern. Whereas normal ductal epithelium did not express CD44v6, CD44v6 expression was observed from the early stage of IPMNs and up-regulated in the progression of IPMNs to invasive carcinoma. CD44v6 expression in intestinal-type IPMNs was significantly lower compared with that in other subtypes. Whereas no correlation was observed between lymph node metastasis and CD44v6 expression in invasive IPM carcinomas, the invasion pattern was significantly correlated to CD44v6 expression. It was concluded that CD44v6 expression might determine the morphology and aggressiveness of IPMN [766].

S100P

Intraductal papillary mucinous neoplasms of the pancreas are subclassified based on morphological features, and different immunohistochemical profiles have been identified in association with the subtypes. It was previously reported that S100P was an early developmental marker of pancreatic carcinogenesis and that there was higher S100P expression in intraductal papillary mucinous neoplasms than in normal pancreatic ductal epithelium. However, there have been no reports on novel diagnostic markers to distinguish

intraductal papillary mucinous neoplasm from nonneoplastic lesions. Surgical specimens of intraductal papillary mucinous neoplasm obtained from 105 patients were investigated using immunohistochemistry. S100P expression was not detected in normal pancreatic ductal epithelium but was detected in all intraductal papillary mucinous neoplasm cells (100 %) with diffuse nuclear or nuclear/cytoplasmic staining. MUC5AC was also expressed in most of the intraductal papillary mucinous neoplasms (102/105; 97 %). Furthermore, S100P was clearly expressed in the invasive component of intraductal papillary mucinous neoplasms (32/32; 100 %), including perineural and lymphatic and minimal invasion. On the other hand, MUC5AC was expressed in only 23 cases of 32 invasive components, which was a significant difference. These data suggest that the S100P antibody may be a useful marker for detecting all types of intraductal papillary mucinous neoplasms [767].

Histological subtyping

Intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas are classified into 4 types-gastric, intestinal, pancreatobiliary, and oncocytic on the basis of their morphology and immunohistochemistry. It was classified IPMNs at one institute and used this classification to determine the clinicopathological features, prognosis, and malignant potential of the 4 types. Sixty-one patients with IPMN who underwent surgery between 2000 and 2007 were evaluated retrospectively. There were 24 tumors of the gastric type, 22 intestinal, 12 pancreatobiliary, and 3 oncocytic. Patients with the intestinal or gastric type had a better prognosis than those with the pancreatobiliary type. The intestinal and pancreatobiliary types had almost the same frequencies of carcinoma, but the intestinal type tended to have a lower frequency of invasive carcinoma than the pancreatobiliary type. Patients with invasive carcinomas derived from intestinal-type IPMNs tended to have a better prognosis than those whose invasive carcinomas were derived from the pancreatobiliary type. It was concluded that the intraductal papillary-mucinous neoplasm of the gastric and intestinal types may have less malignant potential than that of the pancreatobiliary type. Invasive carcinomas derived from intestinal-type IPMNs may be less invasive and slower growing than those derived from the pancreatobiliary type [768].

Branch duct or main duct?

Most cystic neoplasms of the pancreas (CNPs) are incidentally discovered. Their management continues to be debated and preoperative diagnosis is often inaccurate. It was performed a retrospective review of 330 patients with incidentally discovered CNPs. Preoperative and final histological diagnoses were correlated. Forty-one percent (136/330) of patients were operated on at diagnosis. Fifty patients underwent resection for a presumed branch-duct (Bd) intraductal papillary mucinous neoplasm (IPMN), which was confirmed in only 64 percent (32/50). Of the remaining patients, 20 percent had main-duct involvement. Mucinous cystic neoplasm was the preoperative diagnosis in 30/136 patients, histologic examination was confirmatory in only 60 percent (18/30). Most lesions presumed to be main-duct or combined IPMNs or serous cystadenomas were confirmed as such after resection (15/16 and 11/12, respectively). Multifocality was not only associated with Bd-IPMN, and 5 percent of all cysts were non-neoplastic. Overall, in only 68 percent of cases did the preoperative and histological diagnoses match. It was concluded that in an experienced, high-volume center, preoperative diagnosis was incorrect in one-third of incidentally discovered CNPs who underwent resection. Of particular concern, 20 percent of presumed Bd-IPMN had a main-duct component. Conversely, 5 percent of resected cysts were not even neoplastic. Clearly, better diagnostic methods are needed to aid in formulating appropriate treatment strategies [769].

Scoring system

The objective of one study was to identify reliable preoperative factors predicting malignancy or invasiveness of intraductal papillary mucinous neoplasm (IPMN) of the pancreas and the effectiveness of a diagnostic scoring system based on these factors. Between 1994 and 2007, 204 patients underwent pancreatic resection for IPMN at a single institute. Medical records were reviewed retrospectively, and a new diagnostic scoring system for predicting malignant IPMN preoperatively was designed. Univariate analysis revealed nine significant predictors of both malignant and invasive IPMN: age \geq 60 years, history of pancreatitis, presence of mural nodule(s), diameter of main pancreatic duct (MPD) >6 mm, main duct or mixed type, total bilirubin >1.2 mg/dl, CA-19-9 >37 U/ml, tumor location in the pancreatic head, and tumor size >30 mm. Multivariate analysis showed that age, pancreatitis, mural nodule(s), and MPD diameter were independent predictors of invasive IPMN, and that all these parameters, plus elevated carbohydrate antigen-19-9 (CA-19-9), were independent predictors of malignant IPMN. A scoring system based on these five factors, each assigned 1 point, and with a cut-off of 3 points, could predict malignant IPMN with a sensitivity of 51 percent and a specificity of 90 percent. The 5-year survival rates of patients with benign and malignant IPMN were 95 percent and 64 percent, respectively [770].

Diagnostics

CT

To assess the conspicuity of invasive carcinomas (solid masses) originating from pancreatic intraductal papillary mucinous neoplasms (invasive IPMNs) and the primary sites of the solid masses on thin-slice dynamic CT 20 patients with pathologically proven invasive IPMNs underwent triple-phase dynamic CT examinations (arterial, portal, and delayed phases). Qualitative and quantitative analyses of conspicuity of the solid masses were performed for all phases. The primary sites (branch duct and/or main pancreatic duct, MPD) of the solid masses were evaluated on CT in comparison to the pathologic findings. The qualitative and quantitative analyses of the conspicuity of the solid masses showed that the arterial phase images were superior to those of the portal and delayed phases. The primary sites of the solid mass were histopathologically diagnosed as branch ducts in 6 (30 %) patients, MPD in 13 (65 %), and both branch ducts and the MPD in one (5 %). The sensitivity and specificity of the CT evaluation of the primary sites were 100 percent for the branch ducts, and for the MPD 93 percent and 100 percent, respectively. It was concluded that arterial phase images are useful for the diagnosis of invasive IPMNs, and attention should be paid to pancreatic parenchyma surrounding the MPD when detecting invasive carcinomas [771].

Recent advances of imaging of early pancreatic cancer including 3D volume data setting in multidetector-row CT (MDCT) and MRI are urging us to focus on the imaging of normal and pathological conditions of pancreatic parenchyme and peripancreatic structures, which are frequently involved by pancreatic cancers and are affecting the prognosis of patients with pancreatic cancers. Five main topics of pancreatic imaging were addressed in one review: pancreatic arterial territories, imaging of the intra- and peripancreatic venous anatomy and its clinical significance, imaging of the peripancreatic lymphatic network and its clinical significance for staging of pancreatic cancer, perfusion characteristics of pancreatic cancer to differentiate chronic mass-forming pancreatitis, and development of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) to adenocarcinoma and pancreatic invasion. Recognition and understanding of the imaging anatomy of the pancreas might lead to precise staging of pancreatic cancer and to new approaches of less-invasive treatment. Follow-up of patients with IPMNs of the pancreas on imaging seems, at this time, to be the most valuable strategy in the high-risk group selection [772].

Intraductal ultrasonography

Successful treatment requires reliable preoperative assessment of the highly variable extension of intraductal papillary mucinous neoplasms (IPMNs). It was aimed to determine the role of intraductal ultrasonography (IDUS) in predicting the extension of IPMN, and in selecting the method of pancreatic resection and the long-term outcome after surgery. It was a randomized prospective study. Forty consecutive patients who underwent IPMN resection were included in the study. Patients were randomly assigned to an IDUS group or control group, in which IDUS was not performed. Preoperative assessment by IDUS had an 85 percent (17 of 20) diagnostic accuracy for tumor extension of IPMN compared with 50 percent (10 of 20) in cases assessed by other imaging methods without IDUS, which was a statistically significant difference. In 9 of 15 patients with invasive carcinoma, the tumor was located in the pancreatic head, and 11 had a main duct-type tumor. Recurrent disease was identified in 5 of 15 (33 %) patients with invasive IPMN at a mean follow-up of 50 months; of them, 1 underwent preoperative IDUS and 4 were assessed by other imaging methods. None of the 25 patients with noninvasive IPMN had recurrent disease at follow-up. The overall cumulative 3-year survival rate was 79 percent. It was concluded that preoperative IDUS was useful in determining the type of surgery and the extent of resection, especially in main-duct IPMN [773].

MUC in pancreatic juice

Some intraductal papillary mucinous neoplasms (IPMNs) have no proliferation to malignant IPMNs, and benign IPMNs can observe the natural course without a surgical intervention. Therefore, an accurate assessment is required to determine the appropriate decision on managing malignant IPMNs. Quantitative real-time reverse transcription-polymerase chain reaction was performed for pancreatic juice by a LightCycler instrument focused on carcinoembryonic antigen, MUC1, and human telomerase reverse transcriptase. MUC1/glyceraldehyde-3-phosphate dehydrogenase messenger RNA (mRNA) ratio in intraductal papillary mucinous carcinoma (IPMC; median, 4710.7) was significantly higher in intraductal papillary mucinous adenoma (IPMA; median, 727). Furthermore, the MUC1/glyceraldehyde-3-phosphate dehydrogenase mRNA ratio in carcinoma in situ and minimum invasive IPMC (median, 26,490) was significantly higher than that in IPMA. The cutoff level of MUC1 ratio was determined as 1600 for the division of IPMC from IPMA by the receiver-operating characteristic curve. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MUC1 mRNA were 89 percent, 71 percent, 80 percent, 83 percent, and 81 percent, respectively. It was concluded that quantitative reverse transcription-polymerase chain reaction using MUC1 is useful for the detection of malignant IPMN in pure pancreatic juice [774].

Prognosis in general

In general, the prognosis of IPMN is much more favorable than that of pancreatic ductal adenocarcinoma (PDAC). However, IPMN has a broad biological spectrum and it sometimes progresses, slowly showing neoplastic transformations. International consensus guidelines have been recently proposed for the management of IPMN. While they significantly contribute to appropriate management of IPMN, various issues including the natural history and malignant potential of IPMN are not fully elucidated. One review focused on the malignant potential, including the postoperative recurrence of IPMN, coincidence of IPMN with PDAC, and extrapancreatic malignancy that may affect the long-term survival of the patients rather than IPMN itself [775].

Risk of malignancy

Although branch duct intraductal papillary mucinous neoplasms of the pancreas (BD-IPMN) are being diagnosed with increasing frequency, the incidence of concomitant pancreatic carcinoma (PC) is not well known. It was investigated the incidence and clinical features of synchronous and metachronous PC in patients with BD-IPMN in 168 BD-IPMN patients diagnosed by various imaging modalities, including endoscopic retrograde pancreatography, between 1990 and 2008. It was reviewed the medical records and clinical features in both patients developing and not developing PC. The diagnosis of PC was histologically verified in all patients. PC was observed in 9 (5 %) of 168 patients. Five were synchronously detected at the time of BD-IPMN diagnosis, whereas four were metachronously identified during the follow-up period. All PCs occurred in regions separate from the BD-IPMN lesion. All PCs represented histologically invasive ductal adenocarcinomas, whereas the BD-IPMN lesion was diagnosed as adenoma. Patients developing PC were significantly older than patients not developing PC. The diameters of the BD-IPMN lesions and main pancreatic ducts were significantly smaller in patients developing PC than patients not developing PC. It was concluded that it is not infrequent for PC to occur in the pancreas with BD-IPMN. Particular attention should therefore be paid to the development of PC, even in low-risk BD-IPMN, as well as to changes in branch duct intraductal papillary mucinous neoplasms of the pancreas [776].

Prognosis at cancer in situ

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas often recurs after operative resection. The absolute risk and incidence of recurrence, however, especially in the remnant pancreas, is unknown. Therefore it was reviewed an 18-year experience of 144 surgical cases of IPMNs and selected 103 cases of benign IPMN and carcinoma in situ (CIS) for analysis of the clinicopathologic features and long-term outcome of the recurrent disease, with particular emphasis on the status of the cut margins of the pancreas. No patient with benign IPMN died within 5 years. Recurrences in the remnant pancreas were observed in 9 cases: 4 (5 %) among the 81 cases of benign IPMNs and 5 (23 %) among the 22 cases of CIS. All recurrences were considered as multicentric because none recurred at the true resection margin of the previous operative resection. The pancreatic transection margin was normal or hyperplastic in 64 patients, whereas adenoma was detected at the margin in 28 patients. The presence of adenoma had no influence on the outcome, and recurrence in the remnant pancreas was diagnosed in 5 (8 %) of 64 adenoma-negative patients and 3 (11 %) of 28 adenoma-positive patients. Furthermore, both overall survival and recurrence-free survival were similar between the 2 groups. It was concluded that in benign IPMN and CIS, a favorable prognosis can be expected irrespective of the status of the pancreatic cut surface, although follow-up with adequate imaging studies is recommended for detection and resection of the recurrent disease [777].

Prognosis versus pancreatic adenocarcinoma

Although invasive intraductal papillary mucinous neoplasm (IPMN) of the pancreas is thought to be more indolent than sporadic pancreatic adenocarcinoma (PAC), the natural history remains poorly defined. The authors compared survival and identify prognostic factors after resection for invasive IPMN versus stage-matched PAC. The Surveillance, Epidemiology, and End Results database (1991-2005) was used to identify 729 patients with invasive IPMN and 8082 patients with PAC who underwent surgical resection. Patients with resected invasive IPMN experienced significantly improved overall survival when compared with resected PAC (median survival, 21 vs 14 months). Stratification by nodal status

demonstrated no difference in survival among lymph node-positive patients; however, median survival of resected, lymph node-negative, invasive IPMN was significantly improved compared with lymph node-negative PAC (34 vs 18 months). On multivariate analysis, PAC histology was an adverse predictor of overall survival (hazard ratio, HR, 1.31; 95 % confidence interval, CI, 1.15 to 1.50) compared with invasive IPMN. For patients with invasive IPMN, positive lymph nodes (HR, 1.98; 95 % confidence interval 1.50 to 2.60), high tumor grade (HR, 1.74; 95 % confidence interval 1.31 to 2.31), tumor size >2 cm (HR, 1.50; 95 % confidence interval 1.04 to 2.19), and age >66 years (HR, 1.33; 95 % confidence interval 1.03 to 1.73) were adverse predictors of survival. It was concluded that although lymph node-negative invasive IPMN showed improved survival after resection compared with lymph node-negative PAC, the natural history of lymph node-positive invasive IPMN mimicked that of lymph node-positive PAC [778].

Prognosis in main duct IPMN

Main duct intraductal papillary mucinous neoplasms (IPMNs) of the pancreas include neoplasms with varying likelihood of progression to malignancy. The aim of one study was to investigate a natural course of main duct IPMNs with a lower likelihood of malignancy. Twenty main duct IPMNs with a lower likelihood of malignancy, which was defined as mural nodule of less than 10 mm or no visualized mural nodule, and negative result of cytological examination of pancreatic juice, underwent regular ultrasound every 3 months. Special imaging examinations and additional pancreatic juice cytological examination were performed when necessary. Surgery was considered when a mural nodule enlarged to 10 mm or the cytological examination result indicated malignancy. During a mean of 70 months, 12 IPMNs (60 %) did not progress and 6 (30 %) progressed within a lower likelihood of malignancy. The remaining 2 IPMNs (10 %) progressed to meet the criteria for resection, underwent surgery, and were demonstrated to be carcinomas. It was concluded that main duct IPMN with a lower likelihood of malignancy was divided into 2 subgroups: neoplasm that progressed and that which did not progress during its natural course. The former should be resected considering its malignant potential, whereas the latter may be managed nonsurgically as long as it stays unchanged [779].

Prognosis in branch duct IPMN

To evaluate the clinical outcomes of conservative management by observation with MRI of patients with branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) 23 consecutive patients, who were followed up by MRI with magnetic resonance cholangiopancreatography (MRCP) over a period of more than 9 months after initial MRI examinations, were enrolled in a study. On MRI, number of lesions, the maximum diameter of BD-IPMNs, lesion location, the presence of associated dilatation of main pancreatic duct (MPD), the presence of enhancing mural nodules within the lesion and the presence of interval change were retrospectively reviewed on initial and follow-up MR images in consensus by two radiologists. All patients were evaluated to search for evidence of malignant progression of disease. The follow-up period ranged from 10 to 96 months (mean, 37 months). On initial MRI with MRCP, a total of 39 lesions were found in 23 patients. The maximum diameter of BD-IPMNs ranged between 6 and 32 mm, with a mean of 12 mm. Thirty-four lesions (87 %) of 19 patients remained unchanged in the maximum diameter. Five lesions (13 %) of four patients showed an increase in the maximum diameter. Enhancing mural nodules were not found in any individual, neither on the initial MRI study nor on the follow-up studies. There was no patient who had evidence of local aggressive growth of tumor or evidence of metastases to distant sites. The study suggests that branch-duct IPMNs

without enhancing mural nodules are essentially benign and should be managed nonoperatively through observation by MRI [780].

Patients with branch duct type intraductal papillary mucinous neoplasm (BD-IPMN) without invasion usually show favorable prognosis. However, the prognosis becomes poor when the IPMN lesions give rise to invasive carcinoma cells. In addition, recent studies have revealed that BD-IPMN is frequently complicated by common type pancreatic ductal carcinoma. Thus, the prognosis of BD-IPMN depends on the occurrence of these two types of invasive carcinoma. However, little is known about the risk factors for the development of these invasive carcinomas in BD-IPMN. One study aimed to identify the factors which predict the development of invasive carcinoma in BD-IPMN. Invasive pancreatic carcinoma associating with BD-IPMN was classified as invasive IPMN group (invasive carcinoma derived directly from IPMN lesions) and concomitant group (common type of invasive carcinoma concomitant with BD-IPMN). The relation between the incidence of each type of invasive carcinoma in BD-IPMN and the clinicopathological parameters was retrospectively analyzed. There were 12 patients with invasive IPMN and 7 patients with concomitant cancer in 159 patients with BD-IPMN. Diameter of dilated branch or main pancreatic duct (MPD), size of mural nodule, serum CEA level and serum CA19-9 level were factors associated significantly with invasive IPMN by univariate analysis. Among these factors, mural nodule with size larger than 6.5 mm (odds ratio 14.9; 95 % confidence interval 1.4 to 60.5) and serum carcinoembryonic antigen (CEA) level over 5 ng/ml (odds ratio 6.9; 95 % confidence interval 1.17 to 54.13) were found to be the factors independently associated with invasive IPMN. On the other hand, both univariate and multivariate analyses revealed that elevated carbohydrate antigen 19-9 (CA 19-9) levels were associated with the occurrence of concomitant ductal carcinoma in BD-IPMN (odds ratio 10.31; 95 % confidence interval 1.77 to 81.51). It was concluded that careful imaging study of the entire pancreas in addition to tumor lesions and measurement of serum CEA and CA19-9 would be required to find out the development of the two types of invasive carcinoma in BD-IPMN [781].

Although branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) are slow-growing tumors with a favorable prognosis, the synchronous occurrence of pancreatic ductal adenocarcinomas (PDAs) in patients with BD-IPMNs has been reported. One study was aimed to elucidate the development of PDAs in long-term follow-up patients with BD-IPMNs. It was investigated 89 BD-IPMN patients who had no mural nodules and followed them up conservatively at least 2 years (median follow-up, 64 months; range, 25-158 months). All subjects underwent examinations by imaging modalities including endoscopic retrograde pancreatography. It was calculated the standardized incidence ratio (SIR) from the vital statistics compiled by the Ministry of Health, Labor, and Welfare of Japan. Among the 89 patients, 4 cases of PDAs distant from BD-IPMN were observed in 552 patient-years of follow-up (7.2 per 1000 patient-years). The expected number was 0.25, and the SIR of PDAs was 15.8 (95 % confidence interval, 4.3 to 40.4). Subgroup analyses showed that the incidence of PDAs was significantly increased in patients 70 years or older (SIR 16.7; 95 % confidence interval 3.4 to 48.7) and in women (SIR 22.5; 95 % confidence interval 2.7 to 81.1). It was concluded that also patients with branch duct-IPMNs are at a high risk for pancreatic adenocarcinoma [782].

In branch duct intraductal papillary mucinous neoplasm of the pancreas, the importance of the cyst size to predict malignancy is still controversial. The aim of one study was to elucidate the malignant potential of branch duct IPMN without mural nodules (flat branch duct IPMN). Seventy-three patients with flat branch duct IPMNs were studied. There were 6 malignant IPMNs in this series, all of which were 30 mm or more in size, whereas there was no malignancy in IPMNs of less than 30 mm. Statistically significant predictors of malignancy were atypical cytological condition and main pancreatic duct (MPD) diameter of 5 mm or more. The cyst size of 30 mm or more tended to be associated with malignancy. The frequency of malignancy in flat branch duct IPMNs with the size of 30 mm or more and MPD

diameter of less than 5 mm was 4 percent, whereas there were 5 malignant cases (26 %) in flat branch duct IPMNs with the size of 30 mm or more and MPD diameter of 5 mm or more. It was concluded that the size criteria (≥ 30 mm) to predict malignancy proposed in the international consensus guidelines is appropriate and resection or meticulous follow-up using cytological examination and MPD dilatation is needed in patients with flat branch duct IPMNs [783].

IPMN and concomitant pancreatic cancer

Despite the recent progress of diagnostic and therapeutic modalities, survival rates of pancreatic adenocarcinoma remain poor, mainly due to late diagnosis. It was reported a case of a 56-year-old man who was diagnosed with a symptomatic intraductal papillary mucinous tumor of the pancreas located in the uncus. This tumor was associated with a concurrent stenosis of the isthmic pancreatic duct which resulted in a distal dilation. A Whipple procedure was performed. During the procedure, a concomitant adenocarcinoma was diagnosed 2 cm from the primary intraductal papillary mucinous tumor, causing the isthmic stenosis. A second resection was then performed to the left of the pancreatic isthmus, and adjuvant chemotherapy was performed. The patient is well and without any sign of recurrence 7 months after surgery. It was discussed the possibility that intraductal papillary mucinous tumors may be a "red flag" enabling earlier diagnosis of a concurrent pancreatic adenocarcinoma arising in another area of the pancreas [784].

Invasive cancer

Invasive ductal carcinoma (DC) of the pancreas arising as an independent lesion in association with intraductal papillary mucinous neoplasm (IPMN) has occasionally been reported. However, clinicopathological features related to the presence of DC in patients with IPMN remain largely unknown. The purpose of one study was to determine the factors predicting the presence of concomitant DC in those with IPMN. It was retrospectively reviewed the clinicopathological data of a consecutive series of 236 patients with IPMN treated by surgical resection or followed up at our institution between 1987 and 2008. Of 236 patients with IPMN, concomitant DC was detected synchronously or metachronously in 22 patients (9 %). All the 22 IPMNs were of branch duct type and histological grades of 12 resected IPMNs were adenoma (n=8) and borderline (n=4). Multivariate analysis revealed 2 significant predictive factors for the presence of DC in IPMN, including significantly worsening diabetes mellitus and an abnormal serum CA 19-9 level. In view of the high prevalence of DC careful inspection of the entire pancreatic gland is necessary for early detection of DC in patients with branch duct IPMNs, especially when worsening diabetes mellitus and an abnormal serum CA 19-9 level are manifested [785].

Recurrent disease

Adjuvant treatment for pancreatic adenocarcinoma has been shown to improve survival. An increasingly recognized "subtype" of pancreatic adenocarcinoma is invasive intraductal papillary mucinous neoplasm (IPMN). It is unclear whether adjuvant treatment for invasive IPMN improves survival. One study aimed to determine the impact of adjuvant treatment in invasive IPMN. It was conducted a retrospective analysis of merged clinical databases including 412 patients undergoing resection for IPMN at two academic institutions between 1989 and 2006. Of 412 patients with IPMN who underwent pancreatectomy, 98 had invasive carcinoma. Median survival in invasive IPMN was 32 months. Adjuvant treatment did not affect median survival in node-positive or node-negative invasive IPMN. Biopsy-proven

recurrence of invasive IPMN occurred in 45 patients (46 %). The median disease-free interval from resection to recurrence was 27 months. Treatment of recurrences with chemotherapy or radiation therapy was not associated with a difference in survival; however, a subgroup of patients with recurrence in the remnant pancreas who underwent re-resection appeared to have more favourable outcomes. It was concluded that an invasive component measuring >2 cm and lymph node involvement are associated with poorer prognosis. Adjuvant therapy in invasive IPMN appears to confer no survival benefit. In selected patients with recurrence of invasive IPMN in the remnant pancreas, re-resection should be considered [786].

The risk factors correlated with the post-operative recurrence of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are not well established. The aim was to determine the risk factors of recurrence. It was reviewed retrospectively the differences of clinicopathologic features between the recurrence and nonrecurrence groups of patients with IPMN who underwent surgical resection and analyzed the recurrence-related factors. A total of 103 patients were confirmed to have IPMNs. The mean postoperative follow-up was 3.2 years, and the recurrence rate was 13 percent. Recurrent cases (n=13) had the following pathologic grades: adenoma, 1; and invasive carcinoma, 12. The mean postoperative survival was 17 months in the recurrence group and 41 months in the nonrecurrence group. The independent risk factors of recurrence were invasive carcinoma (hazard ratio = 72; 95 % confidence interval 2.13 to 2417), elevated carbohydrate antigen 19-9 (hazard ratio = 38, 95 % confidence interval 2. to 542), and main location in the pancreatic head (hazard ratio = 0.16, 95 % confidence interval 0.03 to 0.90). It was concluded that the risk factors associated with recurrence of IPMNs were invasive pathology, elevated carbohydrate antigen 19-9, and main location in the pancreatic head. A more careful follow-up is needed for such patients [787].

Extrapancreatic manifestations

One study was performed to describe the possible presence of extrapancreatic neoplasms in patients with intraductal papillary mucinous neoplasm (IPMN) and to evaluate whether the extrapancreatic tumours were synchronous or metachronous to IPMNs. One hundred and forty-two patients (56 men and 86 women; mean age 70 years, range 37-98) with IPMN diagnosed using the Sendai criteria were enrolled. Six patients (4 %) had type I, 103 (73 %) type II and 33 (23 %) type III IPMN. All patients were studied using the following imaging techniques: ultrasonography (US), multidetector computed tomography (MDCT) and magnetic resonance cholangiopancreatography (MRCP). Pancreatic IPMN was localised in the head in 43 patients (30 %), in the body in 13 (9 %), in the tail in ten (7 %), in the head-body in 17 (12 %), in the body-tail in 15 (11 %), and diffuse throughout the gland in 44 (31 %). The mean size of the cystic lesions was 1.9 ± 1.9 cm (range 0.5-8.0 cm). Twenty patients (14 %) had associated pancreatic or extrapancreatic diseases. In evaluating the distribution of pancreatic or extrapancreatic diseases according to IPMN type, it was found that this was not significantly different among types I, II and III. It was thus concluded that the majority of pancreatic and extrapancreatic cancers occur before the diagnosis of IPMNs is made and is not related to the type of IPMN [788].

Several studies have reported an increased risk of extrapancreatic neoplasms in patients with IPMN, but these studies focused only on those patients who underwent resection and excluded those patients treated nonoperatively. Therefore it was estimated the frequency of extrapancreatic neoplasms in patients with IPMN compared with those with ductal pancreatic cancer and a general referral population. All patients diagnosed with IPMN at Mayo Clinic from 1994 to 2006 were identified. Two control groups consisting of group 1-patients with a diagnosis of ductal pancreatic adenocarcinoma (1:1) and group 2-a general referral population (3:1) were matched for gender and age at diagnosis, year of registration, and

residence. Logistic regression was used to assess the risk of a diagnosis of extrapancreatic neoplasms among cases versus controls. There were 471 cases, 471 patients in group 1, and 1413 patients in group 2. The proportion of IPMN patients having any extrapancreatic neoplasm diagnosed before or coincident to the index date was 52 percent (95 % confidence interval 47 to 56 %), compared with 36 percent (95 % confidence interval 32 to 41 %) in group 1, and 43 percent (95 % confidence interval 41 % to 46 %) in group 2, both significantly different. Benign neoplasms most frequent in the IPMN group were colonic polyps (n=114) and Barrett's neoplasia (n=18). The most common malignant neoplasms were nonmelanoma skin (n=35), breast (n =24), prostate (n=24), colorectal cancers (n=19), and carcinoid neoplasms (n=6). It was concluded that patients with IPMN have increased risk of harboring extrapancreatic neoplasms. Based on the frequency of colonic polyps, screening colonoscopy should be considered in all patients with IPMN [789].

Acute pancreatitis in IPMN

Acute pancreatitis (AP) may reveal intraductal papillary mucinous neoplasms of the pancreas (IPMN). The aims of one study were to describe the characteristics of AP associated with IPMN and to compare patients with AP with those without AP. All patients who underwent surgery for IPMN between 1995 and 2006 were retrospectively studied. Clinical, imaging, and histological data were collected. The clinical and radiological severity of AP, the number of episodes, and recurrence after surgery were assessed. One hundred eighty-five patients were included. Sixty-four (35 %) had at least one bout of acute pancreatitis (median, 2; range, 1-10). The median Balthazar score was 1 (0-6). Imaging analysis showed no difference between the two groups except for the presence of a mass. Branch duct IPMNs were more frequent in the AP group (74 % vs 45 %), whereas combined IPMNs were more frequent in the non-AP group (45 % vs 22 %). There was no difference in the grade of dysplasia between AP and non-AP groups: carcinoma, 45 percent versus 56 percent; benign IPMN, 55 percent versus 44 percent, respectively. It was found that acute pancreatitis occurs in up to one third of patients with IPMNs. Acute pancreatitis is not severe and often recurs [790].

Post-ERCP-pancreatitis in IPMN

The objective of one study was to evaluate the efficacy of a pancreatic stent regarding the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis after aspiration of pure pancreatic juice in patients with intraductal papillary mucinous neoplasms. A retrospective study was made to assess the outcome in 121 consecutive patients with intraductal papillary mucinous neoplasms who underwent endoscopic aspiration of pure pancreatic juice for cytologic examination between 2001 and 2007. From 2001 to 2004, 58 patients did not undergo pancreatic stent insertion (the no-stent group). The remaining 63 patients did undergo stent insertion (stent group). The overall incidences of post-ERCP pancreatitis were 11 (9 %). The incidences of post-ERCP pancreatitis in the stent and non-stent groups were 8 (13 %) and 3 (5 %), respectively. In the male patients and the patients with a smaller diameter of the main pancreatic ducts, post-ERCP pancreatitis was seen more frequently in those in the stent group (13 % and 21 %, respectively) than in those in the non-stent group (0 % and 0 %). It was concluded that a pancreatic stent did not seem to decrease the incidence of post-ERCP pancreatitis in patients with intraductal papillary mucinous neoplasms. Furthermore, the pancreatic stent seems to be potentially detrimental in male patients and in patients with small-diameter main pancreatic ducts [791].

In pancreas divisum

The diagnosis of benign tumors, including the IPMT, complicating pancreas divisum is very rare. Here, it was presented what we believe is the first case of two simultaneous IPMTs arising from the dorsal and ventral ducts in pancreas divisum. A 74-year-old woman was admitted for recurrent episodes of mild rectal bleeding in the past 2 to 3 months. The patient was asymptomatic, but laboratory tests showed severe sideropenic anemia, requiring transfusion. During hospitalization, a routine abdominal ultrasound discovered a hypoechoic lesion of the pancreas. An abdominal computerized tomography confirmed a fluid lesion in the presence of normal pancreatic volume without calcifications. A complete pancreas divisum was documented by the absence of communication between the MPD and the Wirsung duct. Furthermore, MRCP revealed the presence of 2 multicystic grapelike dilatations of the branch ducts: the first in the dorsal pancreas arising from the MPD and the second in the ventral pancreas arising from the Wirsung duct. Both lesions have been diagnosed as branch duct-type IPMTs. This case suggests that IPMTs in pancreas divisum can occur simultaneously in both ducts and may remain asymptomatic [792].

Adjuvant therapy

Intraductal papillary mucinous neoplasms are mucin-producing cystic neoplasms of the pancreas. One-third is associated with invasive carcinoma. It was examined the benefit of adjuvant chemoradiotherapy (CRT) for this cohort. Patients who had undergone pancreatic resection at Johns Hopkins Hospital between 1999 and 2004 were reviewed. Of these patients, 83 with a resected pancreatic mass were found to have an intraductal papillary mucinous neoplasm with invasive carcinoma, 70 of whom met inclusion criteria for the present analysis. The median age at surgery was 68 years. The median tumor size was 3.3 cm, and invasive carcinoma was present at the margin in 16 percent of the patients. Of the 70 patients, 50 percent had metastases to the lymph nodes and 64 percent had Stage II disease. The median survival was 28 months, and 2- and 5-year survival rate was 57 percent and 45 percent, respectively. Of the 70 patients, 40 had undergone adjuvant CRT. Those receiving CRT were more likely to have lymph node metastases, perineural invasion, and Stage II-III disease. The 2-year survival rate after surgery with versus without CRT was 56 percent versus 59 percent, respectively. Patients with lymph node metastases or positive surgical margins benefited significantly from CRT. On multivariate analysis, adjuvant CRT was associated with significantly improved survival, with a relative risk of 0.43 (95 % confidence interval, 0.19 to 0.95) after adjusting for major confounders. It was concluded that adjuvant chemoradiotherapy conferred a 57 percent decrease in the relative risk of mortality after pancreaticoduodenectomy for intraductal papillary mucinous neoplasms with an associated invasive component after adjusting for major confounders. Patients with lymph node metastases or positive margins appeared to particularly benefit from CRT after definitive surgery [793].

Quality of life after surgery

Uncertainties remain over whether prophylactic surgery or surveillance is the better management option for intraductal papillary mucinous neoplasm of the pancreas. The aim of one preliminary study was to determine if differences in anxiety and quality of life exist between patients who have surgery or undergo surveillance. Recruited patients were given the Hospital Anxiety and Depression Scale, a general survey that evaluates anxiety, and the Functional Assessment of Cancer Therapy-Pancreas, a disease-specific survey that assesses quality of life. Questionnaires were scored by standardized algorithms and compared using Student's t test or Wilcoxon rank-sum test. Sixteen patients had surgery and

16 patients were undergoing surveillance. Mean age was 67 + 20 years. Responses from both groups were remarkably similar. Surgery patients scored higher on the anxiety questionnaire than surveillance patients, although not statistically significant. Surgery patients scored significantly lower on the functional well-being domain of the quality-of-life instrument, though there were no differences in overall quality of life. The authors concluded that prophylactic surgery does not reduce quality of life, and a protocol of surveillance does not appear to generate undue anxiety in this select patient group. Further investigation with more patients is required to validate these findings [794].

Experimental

Xenograft model

In one study, it was described a novel xenograft model and cell culture created to biologically and genetically characterize these tumors. Xenograft mice and cell lines were created from IPMC. Global genomic changes were evaluated by cytogenetic analysis and array comparative genomic hybridization. Specific mutations and sonic hedgehog (Shh) pathway activity were examined and xenografts evaluated for sensitivity to anti-Shh therapy. Cytogenetic analysis showed a tetraploid karyotype with multiple aberrations. KRAS and p53 mutations and overexpression of the Shh pathway were identified. Array comparative genomic hybridization revealed multiple chromosomal aberrations comparable with previously published data in IPMNs. Murine xenograft tumors were sensitive to anti-Shh treatment. It was concluded that characterization of IPMC cell lines and xenografts reveals similarities to previously published data on IPMN [795].

SCID mice

Intraductal papillary mucinous neoplasms (IPMNs) are one of the three known curable precursor lesions of invasive pancreatic ductal adenocarcinoma, an almost uniformly fatal disease. Cell lines from IPMNs and their invasive counterparts should be valuable to identify gene mutations critical to IPMN carcinogenesis, and permit high-throughput screening to identify drugs that cause regression of these lesions. To advance the study of the biological features of IPMNs, it was attempted in vivo and in vitro growth of selected IPMNs based on the hypothesis that IPMNs could be grown in the most severely immunodeficient mice. We examined 14 cases by implanting them into nude, severe combined immunodeficient (SCID), and NOD/SCID/IL2Rgamma(null) (NOG) mice, in addition to direct culture, to generate tumor xenografts and cell lines. One sample was directly cultured only. Thirteen tumors were implanted into the three types of mice, including 10 tumors implanted into the triple immunodeficient NOG mice, in which the majority (8 of 10) grew. This included five IPMNs lacking an invasive component. One of the explanted IPMNs, with an associated invasive carcinoma, was successfully established as a cell line. Tumorigenicity was confirmed by growth in soft agar, growth in immunodeficient mice, and the homozygous deletion of p16/cdkn2a. Epithelial differentiation of the cell line was documented by cytokeratin expression. Patient origin was confirmed using DNA fingerprinting. Most non-invasive IPMNs grow in NOG mice [796].

Cell line

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are a unique entity with malignant potential. Histologically, pancreatic ductal adenocarcinoma (PDAC) arising in IPMN (intraductal papillary mucinous carcinoma, IPMC) appears similar to sporadic PDAC; biologically, however, IPMC seems to have a less aggressive clinical course. Little is known about the genetic signature of IPMC. In one study, it was described a novel xenograft model

and cell culture created to biologically and genetically characterize these tumors. Xenograft mice and cell lines were created from IPMC. Global genomic changes were evaluated by cytogenetic analysis and array comparative genomic hybridization. Specific mutations and sonic hedgehog (Shh) pathway activity were examined and xenografts evaluated for sensitivity to anti-Shh therapy. Cytogenetic analysis showed a tetraploid karyotype with multiple aberrations. KRAS and p53 mutations and overexpression of the Shh pathway were identified. Array comparative genomic hybridization revealed multiple chromosomal aberrations comparable with previously published data in IPMNs. Murine xenograft tumors were sensitive to anti-Shh treatment. It was concluded that characterization of IPMC cell lines and xenografts reveals similarities to previously published data on IPMN. In comparison to PDAC, moreover, these data reveal shared aberrations and distinct genomic changes [797].

OTHER PANCREATIC CYSTIC NEOPLASMS

Cystic pancreatic lesions are often discovered incidentally as an asymptomatic finding, at a rate which is increasing considerably. In recent years the understanding of such tumors has become clearly differentiated. The spectrum of relevant lesions includes in particular the intraductal papillary mucinous neoplasm (IPMN), serous cystic neoplasm (SCN) and mucinous cystic neoplasm (MCN). With certain knowledge of their histological and radiomorphological structure as well as their distribution in terms of location, age and sex, such tumors are easy to differentiate and demarcate from common pancreatic pseudocysts. This also implies the fundamental understanding of complementary endoscopic procedures such as endosonography, which enables aspiration of the content of the cyst. A number of cystic pancreatic lesions have the potential to undergo malignant transformation along the adenoma-carcinoma sequence and therefore necessitate a differentiated approach to their radiological management. One review aimed to develop a broad understanding of the pathological and radiomorphological characteristics of cystic pancreatic lesions and provides advice regarding procedures, particularly with respect to incidentally detected lesions [798].

Pancreatic cystic neoplasms are increasingly identified and their management remains uncertain. Recent studies demonstrate an evolving clinical approach. The vast majority of asymptomatic pancreatic cysts without concerning clinical or imaging features can be observed without surgery. Clinical predictors for malignancy at surgery include male sex, age above 50 years, weight loss, and high cyst fluid carcinoembryonic antigen (CEA), but these factors are insufficient for patient selection. Endoscopic ultrasound (EUS)-guided fine needle aspiration with cyst fluid analysis for risk stratification and selective resection appears the most cost-effective approach. In addition to CEA, DNA analysis, differential protein expression, and proteomic studies of cyst fluid may be helpful in differentiating cystic lesions in selected patients. EUS-guided ethanol lavage of cysts resulted in regression; this method may have a role in treatment in the future. More future research investigating the safety of this procedure, technique modifications, and choice of agent is needed. The approach to incidentally discover pancreatic cystic lesions is challenging due to the difficulty in preoperative definitive lesion characterization. Recently developed diagnostic and treatment strategies show promise for improved patient outcomes [799].

The management of incidental pancreatic cysts is not well established because of lack of information on their natural history. International Consensus Guidelines advocate observation of asymptomatic patients with small lesions, despite limited data to support this approach. It was therefore characterize clinical outcomes in a cohort of asymptomatic patients with incidental pancreatic cysts who underwent endoscopic ultrasound (EUS) evaluation \pm fine needle aspiration (FNA). Overall, 317 patients underwent EUS for evaluation of pancreatic cysts from 1995 to 2005. A total of 97/317 (31 %) had asymptomatic, incidentally discovered pancreatic cysts; of 97 asymptomatic patients, 93 were contacted. Of these patients, 71/93 (76 %) had lesions <3 cm and benign EUS features. All were followed without operative therapy. The mean follow-up was 44 months (range, 6-123). A total of 69/71 (97 %) were alive and free of symptoms of pancreatic disease; 2 patients died of unrelated causes. Among these 71 patients with lesions <3 cm, FNA was performed in 33 patients and cytology was negative for malignant cells in all. Overall, 45/71 patients had either follow-up cross-sectional imaging or EUS. All of them had stable lesions. Surveillance studies were performed with a mean follow-up of 28 months (range, 4-120). The 22 patients with lesions >3 cm and/or concerning EUS features underwent resection. Pathologic analysis revealed that 2/22 patients had adenocarcinoma and that 60 percent had premalignant lesions. Endoscopic ultrasound is helpful in evaluation of patients with small incidental pancreatic cystic lesions. Asymptomatic cysts with benign

radiographic and/or endosonographic features may safely be followed clinically and with serial imaging [800].

Cystic neoplasms of the pancreas have been recognized for almost two centuries, but the principles of management continue to evolve. Clinicians have a better understanding now of the diverse pathologies and behaviors of cystic neoplasms, and can characterize them more precisely into benign, malignant, and of uncertain potential in their manifestations. Treatment is dependent on accurate diagnosis and tailored to the potential aggressiveness of the lesion, the surgical fitness of the patient, and the probability of effecting long-term palliation or survival of the patient. In one article the authors reviewed the classification based on the World Health Organization classification and the latest evidence-based literature of cystic neoplasms, and present their considerations for surgical management of the various lesions. A better understanding of the biologic potential of cystic neoplasms such as intraductal papillary mucinous neoplasms allows for a more patient-specific evidence-based management plan [801].

In recent years there has been an increase in the diagnosis of cystic tumors of the pancreas. In this setting, difficult diagnostic problems and different therapeutic management can be proposed. A review of the literature and authors experience was undertaken. Cystic tumors of the pancreas include different neoplasms with a different biological behaviour. While most serous cystadenomas (SCAs) can be managed nonoperatively, patients with mucinous cystic neoplasms (MCNs), solid pseudopapillary tumors (SPTs), main-duct intraductal papillary mucinous neoplasms (IPMNs) should undergo surgical resection. Branch-duct IPMNs can be observed with radiological and clinical follow-up when asymptomatic, < 3 cm in size and without radiologic features of malignancy (i.e. nodules) [802].

Double tumors

Cystic neoplasms account for less than 10 percent of all pancreatic neoplasia. They are either primarily cystic or result from the cystic degeneration of solid tumors. Most of these are composed of 3 main tumor types: serous cystadenoma, mucinous cystic neoplasms, and intraductal papillary mucinous neoplasms. Solid pseudopapillary tumors of the pancreas (SPT) account for less than 10 percent of cases and are relatively indolent, with an excellent prognosis even in the presence of metastases. Pancreatic intraepithelial neoplasias (PanINs) are thought to be premalignant tumors that range in severity from PanIN-1A to PanIN-3 (carcinoma in situ). Survival is dependent on the size and stage of the tumor. It was reported an unusual case where a young woman was found to have two histologically different tumors. A 29-year-old woman presented with a 6-month history of intermittent epigastric pain, which had not improved with proton pump inhibition. Further history revealed a 2-kg weight loss but no other associated symptoms. There was no significant medical or family history, and examination was unremarkable. Abdominal ultrasound revealed two distinct cysts arising from the body and tail of the pancreas. A computed tomographic (CT) scan confirmed the presence of 2 noncontiguous cystic masses within the body and tail of the pancreas with splenic vein compression with associated gastrosplenic varices. The pancreatic duct could not be seen on the CT. An endoscopic ultrasound was performed and confirmed 2 cystic masses measuring 8.5 cm and 5.5 cm, respectively. The larger (medial) mass was composed of both cystic and solid components, whereas the small (lateral) mass was entirely fluid filled. Neither mass invaded any of the surrounding structures, although there was some vascular compression noted. The patient declined fine-needle aspiration of these cysts. At operation, a giant cystic tumor was seen arising from the body of the pancreas and causing displacement of the surrounding tissues and vessels. Two additional cysts were identified in the atrophic pancreatic tail. The splenic vein was compressed, but not infiltrated, by the primary cystic lesion, and multiple collateral vessels were seen. A spleen-preserving distal pancreatectomy was undertaken, and full laparotomy confirmed the

absence of any peritoneal disease. Postoperative recovery was unremarkable. Histological examination confirmed the presence of two cystic structures measuring 80 mm and 75 mm, respectively. The larger cyst was composed of uniform polygonal cells arranged in sheets and was confirmed as a solid pseudopapillary tumor. The second cyst was separate from the first and histologically different, being composed of columnar cells with low-grade PanIN. No high-grade dysplasia or invasive malignancy was seen in either specimen, and the resection margins were clear. Two reactive lymph nodes were also identified [803].

Biomarkers

Cystic lesions of the pancreas are increasingly being recognized due to the widespread use of high resolution abdominal imaging. Since certain cyst types are precursors to invasive cancer, this situation presents an opportunity to intervene prior to malignant progression. Effective implementation of that strategy has been hampered by difficulties in clearly distinguishing cystic lesions with no malignant potential from those with malignant potential. Here we explored whether glycosylation variants on specific proteins in cyst fluid samples could serve as biomarkers to aid in this diagnosis. It was used a novel antibody-lectin sandwich microarray method to measure the protein expression and glycosylation of mucin (MUC)1, MUC5AC, MUC16, carcinoembryonic antigen, and other proteins implicated in pancreatic neoplasia in cyst fluid samples. Fifty-three cyst fluid samples were obtained from patients with mucinous cystic neoplasms (n=17), intraductal papillary mucinous neoplasms (n=15), serous cystadenomas (n=12), or pseudocysts (n=9), with confirmation of histologic diagnosis at surgical resection. The detection of a glycan variant on MUC5AC using the lectin wheat-germ agglutinin discriminated mucin-producing cystic tumors (mucinous cystic neoplasms+intraductal papillary mucinous neoplasms) from benign cystic lesions (serous cystadenomas+pseudocysts) with a 78 percent sensitivity at 80 percent specificity, and when used in combination with cyst fluid CA 19-9 gave a sensitivity of 87 percent at 86 percent specificity. These biomarkers performed better than cyst fluid carcinoembryonic antigen (37%/80% sensitivity/specificity). These results demonstrate the value of glycan variants for biomarker discovery and suggest that these biomarkers could greatly enhance the accuracy of differentiating pancreatic cystic tumors. Validation studies will be required to determine the clinical value of these markers [804].

Differential diagnosis

Major advances in the last decade have led to an improved understanding of the various types of pancreatic cystic lesions and their biologic behavior. Despite significant improvement in imaging technology and the advent of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) the diagnosis and management of pancreatic cystic lesions remains a significant clinical challenge. Previous "operate in all cases of pancreatic cyst" strategies have been refined and largely replaced using EUS and cyst fluid analysis as the crux for a more practical management approach. The first diagnostic step remains the differentiation between pancreatic pseudocyst and cystic neoplasm. If a pseudocyst has been effectively excluded, the cornerstone issue becomes to determine the malignant potential of the pancreatic cystic neoplasm. In most cases the correct diagnosis and successful management is based not on a single test but on incorporating data from various sources including patient history, radiologic studies, endoscopic evaluation, in particular EUS, and cyst fluid analysis obtained during fine-needle aspirate [805].

Contrast-enhanced ultrasonography

Contrast enhanced ultrasound (CEUS) has been established for detection and characterisation of liver tumours and differential diagnosis of solid pancreatic lesions. The role of transabdominal CEUS in cystic pancreatic disease is less obvious. It was prospectively evaluated CEUS for characterization of undetermined cystic pancreatic lesions with respect to the differential diagnosis of pseudocysts and cystic neoplasia and differentiation between benign and malignant disease (gold standard: histology or cytology). One-hundred and fourteen patients (63 males, 51 females; median age: 62 years, range: 33-87 years) were prospectively examined with conventional B-mode and transabdominal CEUS. Conventional B-mode (criteria: solid nodules, septae), and contrast enhancing features of cystic pancreatic lesions (microperfusion of solid nodules) were analysed. Final diagnoses were made by surgery (47 patients) or histology/cytology and follow-up of at least one year (67 patients). Fifty patients proved to have neoplastic lesions (37 malignant, 13 of benign origin). Sixty-four patients had pseudocysts caused by acute (27 patients) or chronic pancreatitis (37 patients). Conventional B-mode had a sensitivity of 94 percent and a low specificity of 44 percent in the differentiation of pseudocysts versus neoplasia. CEUS had a higher specificity of 77 percent with the same sensitivity of conventional B-mode ultrasound. The combination of conventional ultrasound and CEUS improved the specificity even more to 97 percent with an unchanged sensitivity. CEUS was not reliable in the differentiation of benign and malignant neoplasia. CEUS improves the differentiation between pseudocysts and pancreatic neoplasia in comparison to the conventional B-mode imaging. The microvascularisation visualised using CEUS even in small nodules (with or without septae) associated with cystic lesions is an indicator for cystic pancreatic neoplasia [806].

EUS

The impact of endoscopic ultrasonography (EUS) on the management of pancreatic cystic lesions remains unclear. The aim of one study was to review the experience of EUS for such lesions within one institution. A retrospective review was undertaken of data collected prospectively over a two-year period within the EUS database. Patients who underwent EUS for suspected pancreatic cystic lesions were identified. Data were collected on demographic variables, EUS findings, the results of EUS-guided fine-needle aspiration (FNA) and the findings on clinical and radiological follow-up. Fifty-nine patients were identified. Two thirds were female. Most lesions were located at the pancreatic head. Median diameter was 25 mm. FNA was performed in 36 cases (61 %). On cytology, six (17 %) showed features of mucinous tumours and five (14 %) showed adenocarcinoma. The remainder contained either non-specific benign cells or insufficient epithelial tissue. Follow-up data on 48 cases (83 %), after a median duration of 15 months, revealed that 15 lesions (31 %) had been resected, including six serous and six mucinous tumours. The level of carcinoembryonic antigen in FNA specimens appeared to be higher in mucinous than in serous neoplasms. Twenty-four lesions had undergone repeat radiological imaging: only three had grown in size. It was concluded that EUS and FNA are useful procedures for assessing pancreatic cystic lesions. Malignant features are demonstrated in only a small minority. The majority of the remainder shows no signs of progression during follow-up [807].

Radiology

To identify clinical, radiographic, and histopathologic characteristics associated with cancer in cystic pancreatic neoplasms and to evaluate the preoperative diagnostic accuracy to predict cancer in such cysts. Retrospective case series of 114 patients with cystic lesions of the pancreas who underwent resection between 1992 and 2006. Eighty-nine patients (78 %)

had benign or premalignant cysts; 25 patients (22 %) had malignant cysts (carcinoma in situ and/or an invasive cancer). The factors most predictive of malignancy were age, presence of symptoms, and a dilated pancreatic duct. Of the symptoms recorded, weight loss and jaundice had the strongest correlation with malignancy. It was correctly predicted the pathological diagnosis (benign vs malignant) for only 39 (67 %) of the 58 patients where a preoperative diagnosis was clearly evident. Endoscopic ultrasound did not seem to improve our ability to preoperatively differentiate benign from malignant cysts. This series confirms that age, the presence of symptoms, and a dilated pancreatic duct on imaging are significantly associated with cancer in pancreatic cysts, and it highlights our inability to consistently make the preoperative diagnosis of cancer. Until more accurate markers of malignancy are available, an aggressive approach to management seems justified [808].

MRI versus EUS

The purpose of one study was to compare the diagnostic performance of MRI and endoscopic ultrasound (EUS) for the characterization of cystic pancreatic lesions and prediction of malignancy. Fifty patients (24 women and 26 men; average age, 57 years) underwent both MRI and EUS. All pancreatic lesions (21 cystic and 29 solid lesions) were proven by histopathologic analysis. Two radiologists retrospectively examined MR images, and a single gastroenterologist reviewed EUS images. The MRI and EUS characterizations of morphologic features of the cystic lesions and predictions of malignancy were evaluated. The prediction of malignancy was done by receiver operating characteristic (ROC) curve analysis. There was no difference between the ability of MRI and EUS to correctly classify lesions as cystic or solid (accuracy, 90-98 % vs 88 %). There was no difference between the sensitivity of MRI and EUS for the characterization of septa (94 % for MRI vs 79 % for EUS), mural nodule (67-58 % for MRI vs 58 % for EUS), main pancreatic duct dilatation (93-86 % for MRI vs 85.7% for EUS), and communication with main pancreatic duct (100% for MRI vs 89 % for EUS). The area under ROC curve values for predicting malignancy showed no statistical significance (0.755-0.774 for MRI vs 0.769 for EUS). It was concluded that MRI and EUS are comparable in the characterization of cystic pancreatic lesions and prediction of malignancy [809].

CEA in cyst fluid

The objective of one study was to evaluate and validate cyst fluid carcinoembryonic antigen (CEA) and amylase in differentiating nonmucinous from mucinous pancreatic cystic lesions (PCLs), benign mucinous from malignant mucinous PCLs, and pseudocysts from nonpseudocysts (amylase only). A retrospective analysis of patients with histologically confirmed PCLs from 1996 to 2007 was performed. Cyst fluid CEA (n=124) and/or amylase (n= 91) were measured and correlated to cyst type. Carcinoembryonic antigen levels, but not amylase, were significantly higher in mucinous versus nonmucinous cysts. The sensitivity, specificity, and diagnostic accuracy of CEA 200 ng/mL or greater for the diagnosis of mucinous PCLs were 60 percent, 93 percent, and 72 percent, respectively. Carcinoembryonic antigen levels did not differentiate benign from malignant mucinous cysts. Whereas amylase levels were significantly higher in pseudocysts than nonpseudocysts, 54 percent of noninflammatory PCLs had a level greater than 250 IU/L, including mucinous cystic neoplasms (median, 6800 IU/L; interquartile range, 70Y25,295 IU/L). Malignant mucinous cysts had significantly lower amylase levels than benign mucinous cysts. It was concluded that cyst fluid CEA and amylase levels are suggestive but not diagnostic in differentiating PCLs. Unlike CEA, amylase may help differentiate benign from malignant mucinous cysts [810].

Fine needle aspiration

Pancreatic cysts are common, however, their diagnosis and classification remains a challenge despite advances in cross-sectional imaging and endoscopic ultrasound with fine needle aspiration (EUS-FNA). To determine the incremental yield of cytologic examination of material obtained from targeted fine needle aspiration ("puncture") of the cyst wall after aspiration of fluid for CEA consecutive patients undergoing EUS-FNA of a pancreatic cyst by two expert endoscopists at a single tertiary care center between 2006 and 2008 were retrospectively reviewed. Standard EUS-FNA of pancreatic cysts was carried out, and after cyst fluid aspiration the cyst wall was punctured and aspirated (CWP) to obtain epithelium for cytologic analysis. The diagnostic yields of carcinoembryonic antigen (CEA) obtained from cyst fluid and of cytology obtained from CWP. CEA greater than 192 ng/mL was considered diagnostic of a mucinous cyst. One hundred seven patients underwent EUS-FNA with CWP. Sixteen (31 %) of 52 patients with CEA <192 ng/mL had cytology positive for mucinous epithelium, whereas 15 (47 %) of 32 cysts with an insufficient amount of fluid for CEA analysis had positive cytology from CWP. The additional, cumulative diagnostic yield for mucinous cysts was therefore, 37 percent. Of 55 cysts diagnosed as mucinous, more (56 %) were diagnosed by CWP cytology alone than by CEA. It was concluded that cyst wall puncture and aspiration during routine EUS-FNA may be a safe, easily applied, and inexpensive technique for improving the diagnostic yield for mucinous cysts of the pancreas [811].

Preoperative diagnosis of malignancy in pancreatic cystic lesions (PCLs) remains challenging. Most non-mucinous cystic lesions (NMCLs) are benign, but mucinous cystic lesions (MCLs) are more likely to be premalignant or malignant. The aim of one study was to assess the sensitivity, specificity, and positive and negative likelihood ratios (LRs) of EUS-FNA-based cytology in differentiating MCLs from non-mucinous PCLs. It was conducted a comprehensive search of MEDLINE, SCOPUS, Cochrane, and "CINAHL Plus" databases to identify studies, in which the results of EUS-FNA-based cytology of PCLs were compared with those of surgical biopsy or surgical excision histopathology. A DerSimonian-Laird random effect model was used to estimate the pooled sensitivity, specificity, and LRs, and a summary receiver-operating characteristic (SROC) curve was constructed. It was included 376 patients from 11 distinct studies who underwent EUS-FNA-based cytology and also had histopathological diagnosis. The pooled sensitivity and specificity in diagnosing MCLs were 0.63 (95 % confidence interval 0.56 to 0.70) and 0.88 (95 % confidence interval 0.83 to 0.93), respectively. The positive and negative LRs in diagnosing MCLs were 4.46 (95 % confidence interval 1.21 to 16.43) and 0.46 (95 % confidence interval 0.25 to 0.86), respectively. The area under the curve (AUC) was 0.89. It was concluded that EUS-FNA-based cytology has overall low sensitivity but good specificity in differentiating MCLs from NMCLs [812].

CEA and cytology

Differentiation between the various pathologies presenting as a cystic pancreatic lesion is clinically important but often challenging. It has previously been advocated the performance of endoscopic ultrasound (EUS) with aspiration and determination of mucin and carcinoembryonic antigen (CEA) content. I was reported the results of an ongoing protocol and determine the relative importance of cyst fluid mucin and CEA for the diagnostic process. The institutions prospectively maintained pancreatic cyst database was accessed to identify patients who had undergone pancreatic EUS and cyst aspiration as part of their evaluation. Only those patients who had subsequently undergone resection were selected, with histopathology being the gold standard for comparison. From 2000 to 2009, 174 patients with pancreatic cystic disease underwent surgery, 121 of whom had an EUS with aspiration attempted at our institution with specimens sent for mucin and CEA. Based on histopathology, 86 mucinous lesions were identified, including 44 cystadenomas, 34

intraductal papillary mucinous neoplasms, 7 mucinous adenocarcinomas, and 1 intraductal oncocytic papillary neoplasm; 42 were nonmucinous lesions. The median cyst CEA levels were significantly higher in the mucinous lesions group at 850 versus 2 ng/mL.

	<i>sensitivity</i>	<i>specificity</i>	<i>PPV</i>	<i>NPV</i>	<i>PDLR</i>	<i>NDLR</i>
mucin alone	0.80	0.40	0.61	0.63	1.33	0.68
CEA alone	0.93	0.43	0.51	0.91	1.63	0.16
cytology alone	0.38	0.90	0.92	0.31	3.67	0.69
mucin or CEA	0.83	0.65	0.87	0.57	2.51	0.26)
mucin or CEA or cytology	0.92	0.52	0.86	0.68	1.91	0.15
mucin + CEA	0.96	0.34	0.25	0.97	1.45	0.12
mucin + cytology	0.25	0.97	0.96	0.29	7.25	0.78)
CEA + cytology	0.12	1.00	1.00	0.26	∞	0.88
mucin + CEA + cytology	0.08	1.00	1.00	0.25	∞	0.92

It was concluded that assessment of cyst mucin and CEA are complementary, with the best profile obtained when both markers are determined along with cytology. This combination provides a good sensitivity, PPV, and NDLR, as well as reasonable PPV and PDNR [813].

Immunohistochemistry of stroma

Serous and mucinous cystic neoplasms (SCNs/MCNs) are the most common true cystic neoplasms of the pancreas and occur more frequently in women. The aim of one study was to characterize the stroma of SCNs to compare its phenotype with that of MCNs. A total of 12 SCNs and 5 MCNs were analyzed immunohistochemically using the following antisera: progesterone receptor (PR), estrogen receptor (ER), inhibin, CD10, and vimentin. Normal pancreatic tissue (17 cases) and ductal adenocarcinomas of the pancreas (3 cases) were used as controls. Eight of 12 patients with SCNs and all 5 patients with MCNs were women. For SCNs, the stroma was sclerotic and paucicellular and showed focal moderate to strong reactivity for PR. Estrogen receptor, CD10, and inhibin were virtually negative. For MCNs, the stroma was more cellular and ovarianlike and showed a larger number of PR-positive cells with focal expression of ER and inhibin. Vimentin was expressed in all stromal cells in both groups. It was concluded that both SCNs and MCNs contain PR-positive stromal cells. In view of the aforementioned clinical and immunophenotypical similarities, it was suggested that in SCNs and MCNs, the stromal framework is similar in origin and/or differentiation [814].

Mucinous cystic neoplasms

Cystic lesions of the pancreas are identified with increasing frequency by modern imaging. The mucinous cystic neoplasm (MCN) is treated with resection for its malignant potential. How much preoperative evaluation is needed before undertaking operation is frequently a diagnostic dilemma. A retrospective review of 32 patients who underwent resection of a MCN between 1994 and 2007 was performed to define the preoperative evaluation and operative treatment of MCN patients. Thirty-two patients (30 women; mean age 49) had histology-proven MCN. Twenty-seven patients had symptomatic cysts (84 %). Five had a history of gallstones and/or acute pancreatitis. All patients were worked up with CT and/or MRI. Endoscopic ultrasound was performed in 14 (44 %) and endoscopic retrograde cholangiopancreatography in six (18 %). Cytology was obtained in 13 (40 %). Pathology revealed 22 benign MCNs (68 %), five malignant MCNs (16 %), and five MCNs with

borderline pathology. Preoperative workup including CT or MRI imaging and cytology suggested MCN as the lesion in 15 patients (46 %). CT features by itself predicted MCN in three patients (9 %). Cytology revealed another six patients (19 %) with possible MCN. In this series, preoperative workup did not identify three of five patients with MCN malignancy. A preoperative diagnosis cannot be made in most patients with MCN. Operative treatment can be based on clinical presentation and CT imaging because endoscopic ultrasound and fine needle aspiration for evaluation may be misleading. Middle-aged women with cystic lesions in the tail of the pancreas without prior gallstone or pancreatitis history most typically fit the profile of the MCN patient [815].

The aim of one study was to elucidate the clinicopathological features and prognosis of mucinous cystic neoplasms (MCNs). It was performed a multi-institutional, retrospective study on a collected series of patients with MCN pathologically defined by ovarian-type stroma. Mucinous cystic neoplasm was confirmed in 156 cases, including 129 adenomas (82 %) and 21 noninvasive (13 %) and 6 invasive carcinomas (4 %). Patients with MCN were exclusively women (98 %) with the mean age of 48 years. All but one MCN were in the pancreatic body/tail region with a mean size of 65 mm. Communication between the cyst and the pancreatic duct was found in 18 %. The 3-, 5-, and 10-year survival rates were 98 percent, 97 percent, and 97 percent, respectively. A significant difference in the survival rates was observed between adenomas and carcinomas and between minimally invasive carcinomas and invasive carcinomas. Cyst diameter and presence of mural nodule were predictive of malignant MCN. It was concluded that mucinous cystic neoplasm is a rare but distinctive pancreatic cystic neoplasm with a favorable overall prognosis. All MCNs should be resected to prevent malignant changes but can be observed for an appropriate time when the lesion is small without the presence of mural nodules [816].

Mucinous cystadenomas

Mucinous cystadenomas of the liver are rare cystic neoplasms. The aim of one study was to assess management of a consecutive series of patients who underwent laparotomy for a suspected cystadenoma or cystadenocarcinoma. Secondly, the origin of ovarian stroma (OS) in mucinous liver cystadenomas was examined during early embryonic development. Patients diagnosed with mucinous liver cystadenomas or cystadenocarcinoma between 1994 and 2009 were included. Pathology specimens of patients who had undergone resection were reviewed for OS. Furthermore, in human embryos, morphology of the peritoneal epithelium and the position of the gonads in relation to the embryonic liver, pancreas and spleen were examined. Fifteen surgically treated patients (13 female, 2 male) with hepatic tumors were eventually diagnosed with mucinous liver cystadenomas (12) or cystadenocarcinomas (3). OS was present in all female patients with mucinous cystadenoma or cystadenocarcinoma. The 2 male patients were rediagnosed as intraductal papillary mucinous neoplasm (IPMN) or cystadenocarcinoma with features of IPMN. In human embryos, preceding their “descent”, the gonads are situated directly under the diaphragm, dorsal to the liver, the tail of the pancreas and the spleen, but separated from these organs by the peritoneal cavity. In contrast to the peritoneal epithelium elsewhere, the cells covering the gonads show an activated morphology. For the diagnosis of mucinous liver cystadenoma, the presence of OS is prerequisite. This may be explained by the common origin of cystadenoma and OS in epithelial cells that cover the embryonic gonads in early fetal life [817].

Mucinous nonneoplastic cyst

Mucinous nonneoplastic cyst of the pancreas is a newly described and rare cystic lesion with unknown histogenesis. It is defined as a cystic lesion lined with mucinous epithelium, supported by hypocellular stroma and not communicating with the pancreatic ducts. It is very challenging to differentiate this lesion from other cystic mucinous neoplasms of the pancreas such as branch-duct intraductal papillary mucinous neoplasm by morphology. In one study, a total of 436 pancreatic specimens resected between 2002 and 2007 in one institution were reviewed. Fifteen (3 %, 15/436) mucinous nonneoplastic cysts were identified. They included 3 males and 12 females, with a median age of 60 years. Forty-six percent of cases (7/15) occurred in pancreatic head, 27 percent (4/15) in neck, 7 percent (1/15) in body, and 20 percent (3/15) in tail. The size of lesions ranged from 0.5 to 3.5 cm in greatest dimension. In most cases (12/15, 80 %), mucinous nonneoplastic cyst was associated or adjacent to acinar-ductal mucinous metaplasia. These morphologic data indicate that mucinous nonneoplastic cyst is not really a rare disease and may originate from acinar-duct mucinous metaplasia histogenetically. Furthermore, apomucin immunostains of mucinous nonneoplastic cyst showed MUC1 expressed in 27 percent (4/15) cases, MUC5AC in 67 percent (10/15 cases), and MUC2 was negative in all cases, whereas intraductal papillary mucinous neoplasm (n=17; 5 main duct type, 12 branch-duct type) showed focal and weak MUC1 positivity in 18 percent (3/17) cases, MUC2 positivity in 71 percent (12/17) cases, and all intraductal papillary mucinous neoplasm (17/17) were MUC5AC positive. The clonality assay with the HUMARA gene revealed that the mucinous nonneoplastic cysts were of polyclonal origin. For the first time, using HUMARA assay, it was demonstrated the nonneoplastic nature of these cysts and further characterized morphologic and immunophenotypic properties that allow differentiation from intraductal papillary mucinous neoplasm [818].

von Hippel-Lindau disease

von Hippel-Lindau disease is an uncommon, multisystem, multitumor disorder that can present in sporadic form but is more commonly inherited as an autosomal-dominant disease with high penetrance. Affected patients are at increased risk for developing multiple synchronous or metachronous benign or malignant, cystic, and vascular neoplasms of various organs. The characteristic neoplasms associated with von Hippel-Lindau are hemangioblastoma of the central nervous system and retina, clear cell renal cell carcinoma, and pheochromocytoma, but other lesions are well recognized. Pancreatic lesions, both primary and metastatic, are common, and several differential diagnostic possibilities must be considered [819].

To assess the impact of imaging on pancreatic lesion management in von Hippel-Lindau disease (VHL) it was reviewed sequential computed tomography (CT) and magnetic resonance examinations (1997-2008) of 33 patients with VHL who had at least 1 pancreatic lesion. One hundred sixty-seven imaging studies demonstrated innumerable simple pancreatic cysts and 58 complex pancreatic masses: 24 were complex cystic and 34 were solid (30 small, i.e. ≤ 2 cm, and 4 large, i.e. > 4 cm). Aggregate annual growth was significant in complex cystic and solid masses (mean, 0.39 cm/y and 0.14 cm/y). Solid mass growth differed by size (small: 0.06 cm/y; large: 1.28 cm/y). Thirteen masses were excised. No patient developed metastases. Arterial-phase CT improved solid mass detection, but 28 percent of studies still underreported the total number. It was concluded that most pancreatic masses in VHL do not require annual surveillance. Arterial-phase CT improves mass detection, but many masses remain prospectively missed [820].

von Hippel-Lindau disease is a progressive, autosomal dominant disorder with multiorgan involvement. There are 2 types of pancreatic lesions from von Hippel-Lindau disease: cystic lesions and endocrine pancreatic tumors. Only the latter type is potentially malignant and may justify pancreatic resection. The differential diagnosis between these two types of lesions can be difficult. It was reported three patients with atypical cystic pancreatic lesions who underwent surgery for suspected malignant tumors [821].

PERIAMPULLARY, NON-PANCREATIC TUMORS

Cancers of the ampulla of Vater, distal common bile duct, and pancreas are known to have dismal prognosis. It is often reported that ampullary cancers are less aggressive relative to the other periampullary carcinomas. It was sought to evaluate predictors of survival for periampullary cancers following pancreaticoduodenectomy to identify biologic behavior. It was reviewed the records of all patients who underwent pancreaticoduodenectomy for periampullary carcinoma between 1992 and 2007. Demographics, treatment, and outcome/survival data were analyzed. Kaplan-Meier survival curves were created and compared by log-rank analysis. 346 consecutive periampullary malignancies (249 pancreatic cancers, 79 ampullary carcinomas, 18 extrahepatic cholangiocarcinomas) treated by pancreaticoduodenectomy were identified. Pancreatic cancer histology correlated with the shortest median survival (17 months), followed by cholangiocarcinoma (18 months) and ampullary carcinoma (44 months). Potential predictors of decreased survival on univariate analysis included site of origin, preoperative jaundice, microscopic positive margin, nodal metastasis, lymphovascular invasion, neural invasion, and poor differentiation. Only nodal metastasis (median 16 vs 30 months) and neural invasion (median 18 vs 48 months) significantly predicted outcome on multivariate analysis. It was concluded that although ampullary cancers have the best prognosis overall, when controlled for tumor stage, only presence of neural invasion and nodal metastasis predict poor survival following pancreaticoduodenectomy. Biological behavior remains the most important prognostic indicator in periampullary cancers amenable to resection, regardless of site of origin [822].

Adhesion molecules

Distant metastasis resulting from carcinoma cell detachment from the primary tumor involves modification of adhesion molecules. One study was conducted to examine the correlation of E-cadherin/beta-catenin expression with survival and recurrence in ampullary neoplasms. Patients with diagnoses of ampullary neoplasms were enrolled in the study. Demographics, operative findings, and histopathological data were collected by retrospective chart review. Expression of E-cadherin and beta-catenin were detected by immunohistochemistry. A total of 110 patients were enrolled in the study. Preservation of membranous staining of E-cadherin was noted in 41 (37 %) patients, aberrant cytoplasmic staining in 48 (44 %) patients, and complete loss in 21 (19 %) patients. Loss of E-cadherin was associated with pancreatic invasion, recurrence, and poor prognosis. Membranous staining of beta-catenin was noted in 65 (59 %) patients, cytoplasmic or nuclear accumulation in 16 (15 %) patients, and complete loss in 29 (26 %) patients. Loss of beta-catenin expression was associated with tumor markers, ulcerative type, liver metastases, and poor prognosis. Pancreatic invasion, lymph node involvement, and loss of beta-catenin expression were predictors of disease recurrence. It was concluded that loss of the E-cadherin/beta-catenin complex is related to poor prognosis in ampullary cancer. Loss of beta-catenin is predictor of recurrence in multivariate analysis [823].

Duodenal tumors

Duodenal cancer

Primary adenocarcinoma of the duodenum is a rare disease. All patients treated for duodenal cancer between 1995 and 2006 were retrospectively evaluated. Tumours arising from the pancreatic head, the papilla of Vater, distal bile duct or tumour infiltration from surrounding organs (apart from the duodenum) were excluded. Eleven (31 %) of the 35 included patients (17 women and 18 men, median age 62 years, range 45-88 years) received a curative

resection (R0 resection), while 24 patients had surgical or endoscopic palliation. Survival following R0 resection was significantly higher than survival in the palliative group. The median survival was 45 months in the R0 group versus 5 months in the palliative group. It was concluded that in a consecutive, but retrospective duodenal cancer population, it was found that only one third of the patients were candidates for a curative resection, and despite microsurgical, radical surgery only one third were alive after five years [824].

Duodenal dystrophy

Duodenal dystrophy is a rare disease, characterized by the chronic inflammation of the aberrant pancreatic tissue in the duodenal wall. Two middle-aged men were admitted with upper abdominal pain of several months duration, periodic nausea and vomiting after meals, intermittent jaundice and weight loss. A diagnosis of cystic dystrophy of the vertical part of the duodenum without chronic inflammation of the orthotopic pancreas was established in both cases by multi-detector computed tomography, magnetic resonance imaging and endosonography. Both patients were successfully treated by two modifications of pancreas-preserving duodenal resections with reimplantation of the bile and pancreatic ducts into the neoduodenum. These cases are a good example of a pancreas-preserving approach to duodenal dystrophy treatment and can be an alternative to the Whipple procedure in cases of mild changes of the orthotopic gland [825].

von Recklinghausen

Gastrointestinal stromal tumor is the most frequent nonepithelial tumor found in the gastrointestinal tract. One important clinical problem is that gastrointestinal stromal tumors, especially the extramural growth type, can be difficult to distinguish from other organ tumors. The case of a patient with an extramural gastrointestinal stromal tumor of the duodenum that mimicked a pancreatic head tumor has previously been reported. It was reported a rare case of a patient with a duodenal gastrointestinal stromal tumor with extramural growth that mimicked a pancreatic neuroendocrine tumor. In this case, the gastrointestinal stromal tumor was also associated with neurofibromatosis type 1 (also known as von Recklinghausen's disease). A 60-year-old Japanese woman with a history of neurofibromatosis type 1 was admitted to our hospital for the treatment of a tumor of her pancreas. She had no symptoms, but an abdominal ultrasonography screening examination had revealed a hypoechoic mass in the head of her pancreas. Laboratory data, including tumor markers, were within the normal ranges, and her insulin and glucagon levels were also within the normal ranges. However, her plasma gastrin level was elevated at 580 pg/mL (30 to 150 pg/mL). A computed tomography examination revealed a hypervascular tumor measuring 14mm in diameter in the head of her pancreas. It was diagnosed the patient as having a pancreatic neuroendocrine tumor and performed a tumor resection with a duodenal wedge resection. Microscopic analysis revealed spindle cell tumors in a trabecular pattern. The patient was finally diagnosed as having a duodenal gastrointestinal stromal tumor of the uncommitted type [826].

Brunner's duodenal hamartoma

To describe the computed tomographic (CT) features of Brunner's gland hamartoma with histopathologic correlation the CT images of 9 patients with pathologically proven Brunner's gland hamartoma were reviewed retrospectively. All patients underwent CT performed on multidetector-row CT scanner with various protocols, all of which included portal venous phase. Brunner's gland hamartomas presented as small (mean, 1.9 cm) Yamada type II or III (67 %, 6/9) polyps with frequent internal cyst (33 %, 3/9). They were isoattenuated on unenhanced CT (83 %, 5/6) and hypoattenuated in portal phase (56 %, 5/9) when compared with the pancreas. Peripheral rimlike enhancement in earlier phase was commonly found (6

7%, 6/9) and most of them enhanced homogeneously in the later phase (100 %, 4/4). In a patient with asymptomatic small submucosal mass in the duodenal first or second portion, hypoattenuated mass with peripheral rimlike enhancement or internal cystic change suggests the possibility of Brunner's gland hamartoma [827].

Distal biliary tract tumors

Intraductal tubulopapillary neoplasm (ITPN)

Intraductal tubulopapillary neoplasm (ITPN) has been recently reported in pancreas. We experienced an unusual intraductal growing bile duct tumor, which showed the same histopathologic and immunostaining profiles as ITPN of pancreas. A 72-year-old female patient visited hospital due to intrahepatic stone. The hilar bile duct tumor was detected and incidental lung mass was found in systemic evaluation. The histopathologic finding of the two biopsy lesions was different. The lung tumor was an adenocarcinoma, and the bile duct tumor showed poorly differentiated carcinoma with eosinophilic cytoplasm. Lung lobectomy and hemihepatectomy were performed under the impression of double primary neoplasms of the lung adenocarcinoma and oncocytic variant of the biliary papillary tumor. However the histopathologic findings and immunostaining profiles of the two resected tumors were the same. Both the lung and bile duct tumors showed a tubulopapillary pattern with high-grade nuclear atypia. Pathologic findings were the same as a recently reported ITPN of the pancreas. Eosinophilic cytoplasm of the bile duct tumor was not oncocytic cytoplasm but pyknotic change due to necrosis. Here, we report the first case of ITPN of the bile duct with lung metastasis. The tumor in this case does not fit with any categories in the current biliary tumor classification. It was speculated that this may be the first case of biliary ITPN [828].

Adjuvants

To analyze the outcome of adjuvant chemoradiotherapy for patients with distal common bile duct (CBD) cancer who underwent curative surgery, and to identify the prognostic factors for these patients 38 patients with adenocarcinoma of the distal CBD underwent curative resection followed by adjuvant chemoradiotherapy 1991-2002. There were 27 men and 11 women, and the median age was 60 years (range, 34-73). Adjuvant radiotherapy was delivered to the tumor bed and regional lymph nodes up to 40 Gy at 2 Gy/fraction with a 2-week planned rest. Intravenous 5-fluorouracil (500 mg/m²/day) was given on day 1 to day 3 of each split course. The median follow-up period was 39 months. The 5-year overall survival rate of all patients was 49 percent. On univariate analysis, only histologic differentiation was significantly associated with overall survival. Tumor size (≤ 2 cm vs >2 cm) had a marginally significant impact on the treatment outcome. However, there was no difference in overall survival rates between T3 and T4 tumors, for which the main determinants were pancreatic and duodenal invasion, respectively. On multivariate analysis, histologic differentiation and tumor size were independent risk factors for overall survival. It was concluded that long-term survival can be expected in patients with distal CBD cancer undergoing curative surgery and adjuvant chemoradiotherapy. Histologic differentiation and tumor size were significant prognostic factors predicting overall survival, whereas duodenal invasion was not [829].

Palliative chemotherapy

A British randomised study of gemcitabine plus cisplatin (GC) combination showed promising results in biliary tract cancer (BTC) patients. In a new study, it was evaluated the efficacy and safety of this combination compared with gemcitabine alone (G) in Japanese BTC patients. Overall, 84 advanced BTC patients were randomised to either cisplatin 25 mg/m² plus gemcitabine 1000 mg/m² on days 1, 8 of a 21-day cycle (GC-arm), or single-agent

gemcitabine 1000 mg/m² on days 1, 8 and 15 of a 28-day cycle (G-arm). Treatments were repeated for at least 12 weeks until disease progression or unacceptable toxicity occurred, up to a maximum of 48 weeks. A total of 83 patients were included in the analysis. For the GC and G-arms, respectively, the 1-year survival rate was 39 versus 31 percent, median survival time 11 versus 8 months, median progression-free survival time 6 versus 4 months and overall response rate 20 versus 12 percent. The most common grade 3 or 4 toxicities (GC-arm/G-arm) were neutropenia (56 %/38 %), thrombocytopenia (39 %/7 %), leukopenia (29 %/19 %), haemoglobin decrease (37 %/17 %) and gamma-GTP increase (29 %/36 %). It was concluded that gemcitabine plus cisplatin combination therapy was found to be effective and well tolerated, suggesting that it could also be a standard regimen [830].

Tumors of the papilla of Vater

Cancer of the papilla of Vater is a relatively rare disease. It is difficult to separate from other periampullary tumours at the time of diagnosis. Recent studies have shown that patients with cancer of the papilla tend to survive longer than patients with pancreatic cancer and cancers of biliary and duodenal origin. The aim of one study was to compare local results with those reported in the international literature. The study included all patients who were referred with cancer of the papilla between 1995 and 2005. The data were collected retrospectively from hospital and departmental databases. Among the 35 patients, 30 underwent operation. A total of 27 had a Whipple resection performed, 26 of whom were radical resections. Three patients had a palliative gastroenteroanastomosis performed. Postoperative mortality was 7 percent, and the 1, 3 and 5-year survival was 74 percent, 59 percent and 43 percent, respectively. Resected patients without lymph node involvement had an estimated 5-year survival of 58 percent. The estimated 5-year survival of over 40 percent in resected patients was comparable with that reported in international studies. It was found a significantly higher 5-year survival in patients without lymph node involvement, and the general prognosis for patients with cancer of the papilla was better than the prognosis reported for other periampullary tumours [831].

There has been no uniform terminology for systematic analysis of mass-forming preinvasive neoplasms (which usually is termed tumoral intraepithelial neoplasia) that occur specifically within the ampulla. It was now provided a detailed analysis of these neoplasms, which was proposed to be referred to as intra-ampullary papillary-tubular neoplasm (IAPN). Three hundred and seventeen glandular neoplasms involving the ampulla were identified through a review of 1469 pancreatoduodenectomies and 11 ampullectomies. Eighty-two neoplasms characterized by substantial preinvasive exophytic component that grew almost exclusively (>75 %) within the ampulla (in the ampullary channel or intra-ampullary portions of the very distal segments of the common bile duct or pancreatic duct) were analyzed. The mean age was 64 years, male/female ratio was 2.4, and mean tumor size was 2.7 cm. The tumors had a mixture of both papillary and tubular growth (each constituting at least 25 % of the lesion) in 57 percent; predominantly (>75 %) papillary in 23 percent, and predominantly (>75 %) tubular in 20 percent. High-grade dysplasia was present in 94 percent of cases, of which 39 percent showed focal (<25 % of the lesion), 28 percent showed substantial (25 % to 75 %), and 27 percent showed extensive (>75 %) high-grade dysplasia. In terms of cell-lineage morphology, 45 percent had a mixture of patterns. However, when evaluated with a forced-binary approach as intestinal versus gastric/pancreatobiliary based on the predominant pattern, 74 percent were classified as intestinal and 26 percent as gastric/pancreatobiliary. Percent sensitivity/specificity of cell-lineage markers were, for intestinal phenotype: MUC2 85/78 and CDX2 94/61; and for gastric/biliarypancreatic: MUC1 89/79, MUC5AC 95/69, and MUC6 83/76, respectively. Cytokeratin 7 and 20 were coexpressed in more than half. In 64 cases (78 %), there was an associated invasive carcinoma. Size of the tumor and amount of dysplasia correlated with the incidence of invasion. Invasive carcinoma was of intestinal-type

in 58 percent and of pancreatobiliary-type in 42 percent. Cell lineage in the invasive component was the same as that of the preinvasive component in 84 percent. All discrepant cases were pancreatobiliary-type invasions, which occurred in intestinal-type preinvasive lesions. The overall survival of invasive cases were significantly worse than that of noninvasive ones (57 % vs 93 %); and 3 years, 69 percent versus 100 percent; and 5 years, 45 percent versus 100 percent, respectively. When compared with 166 conventional invasive carcinomas of the ampullary region, invasive IAPNs had significantly better prognosis with a mean survival of 51 versus 31 months and the 3-year survival of 69 percent versus 44 percent. It was concluded that tumoral intraepithelial neoplasia occurring within the ampulla are highly analogous to pancreatic or biliary intraductal papillary and tubular neoplasms as evidenced by their papillary and/or tubular growth, variable cell lineage, and spectrum of dysplastic change (adenoma-carcinoma sequence), and thus it was proposed to refer to these as IAPN. IAPNs are biologically indolent; noninvasive examples show an excellent prognosis, whereas those with invasion exhibit a malignant but nevertheless significantly better prognosis than typical invasive ampullary carcinomas unaccompanied by IAPNs. Twenty eight percent (64 of 230) of invasive carcinomas within the ampulla arise in association with IAPNs [832].

To define the differential imaging features of pancreatobiliary- and intestinal-type ampullary carcinomas at magnetic resonance (MR) imaging and to correlate these features with pathologic findings 50 patients with surgically confirmed ampullary carcinoma and preoperative MR results were studied. Two radiologists, blinded to histologic type of cancer, evaluated imaging findings in consensus. Univariate and multiple logistic regression analysis were performed to define imaging findings that were useful for differentiation of the two types of carcinomas. On the basis of hematoxylin-eosin and immunohistochemical staining, 35 patients were classified as having pancreatobiliary type; and 15 patients, intestinal type. At MR, all of 15 intestinal carcinomas were nodular, whereas 16 (46 %) of 35 pancreatobiliary carcinomas were infiltrative. Intestinal carcinomas were isointense (13 [87 %] of 15) to hyperintense (two [13 %] of 15), whereas 34 percent (12 of 35) of pancreatobiliary carcinomas manifested as hypointense compared with the duodenum on T2-weighted MR images, which was a significant difference. Intestinal carcinoma commonly manifested with an oval filling defect at the distal end of the bile duct on MR cholangiopancreatographic (MRCP) images (11 [73 %] of 15 vs four [11 %] of 35 in pancreatobiliary type). At endoscopy, intestinal carcinoma manifested with an extramural protruding mass (n = 15, 100 %) with a papillary surface (n=11, 73 %), whereas pancreatobiliary carcinoma manifested with intramural protruding (n=5, 28 %) or ulcerating (n=1, 6 %) gross morphologic features with a nonpapillary surface (n=17, 94 %). Multiple logistic regression analysis showed that an oval filling defect at the distal end of the bile duct was the only independent finding for differentiating intestinal from pancreatobiliary carcinoma. An oval filling defect at the distal end of the bile duct on MRCP images and an extramural protruding appearance with a papillary surface at endoscopy are likely to suggest intestinal ampullary carcinoma [833].

OTHER RARE TUMORS IN THE PANCREATIC REGION

Limited data are available to guide the management of very rare exocrine neoplasms of the pancreas (VREP). Available evidence suggests that VREP have different risk factors and prognoses from those of adenocarcinoma of the pancreas. The primary objectives for one study were to determine the survival, comorbidities, and response to treatment of patients seen at Mayo Clinic with VREP. It was reviewed patients from 1975 to 2005 who had VREP and compared them to patients with adenocarcinomas that were matched for TNM, grade, and decade of treatment. Sixty-six patients with VREP were identified. The most commonly identified neoplasms were acinar cell carcinoma (n=15), small cell carcinoma (n=12), and squamous cell carcinoma (n=8). Abdominal discomfort and jaundice were the most common presenting symptoms. The median overall survival for patients with VREP, 10 months (range 4-23 months), was significantly better than that for matched controls, 8 months (range, 4-15 months). There was no difference in the survival of patients with stage 4 disease between cases, 8 months (range 2-22 months), and controls, 7 months (range 2-11 months) (P = 0.17). It was concluded that the overall survival of all patients with VREP was better than matched controls, but no statistical difference was seen between the groups with stage 4 disease [834].

Solid pseudopapillary pancreatic tumor

Solid pseudopapillary tumors of the pancreas (SPT) are rare neoplasms, and the natural history is poorly defined. The aim of one study was to define the natural history and compare patient and tumor factors between patients with malignant and non-malignant disease. Data for all patients with SPT who underwent surgical exploration between 1987 and 2009 were collected and analyzed. Patient, tumor, treatment, and survival variables were examined. Malignant tumors were defined as any tumor that was locally unresectable, metastatic, or recurrent. Forty-five patients had an SPT during the study period. Median age was 38 years (10-63) and 38 (84 %) were women. At the time of diagnosis, 38 were symptomatic, with the most common symptom being abdominal pain (n=35). The most frequent imaging characteristic was a solid and cystic tumor (n=29), most commonly located in the tail of the pancreas (n=23). Resection of the primary tumor (n=41) (41/2,919 = 1.4 % of all resections) included distal pancreatectomy in 26, pancreatoduodenectomy in 11, central pancreatectomy in two, and enucleation in two. Nine patients had malignant disease defined by a locally unresectable tumor in three, liver metastases in three, locally unresectable tumor and liver metastases in one, local recurrence and liver metastases in one, and local recurrence in another. Patients with malignant disease presented with significantly larger tumors (7.8 vs 4.2 cm). After median follow-up of 44 months, 34 patients were without evidence of disease, four patients were alive with disease, three patients died of disease, and four patients died of other causes. These results demonstrate that SPT occurs in young women, and the majority of patients will experience long-term survival following resection. The only feature associated with malignant disease was tumor size at presentation. The majority of patients are alive at last follow-up, and a low percentage experienced disease recurrence or death from disease [835].

The aim of one study was to describe the endoscopic ultrasound (EUS) features and utility of EUS-guided fine needle aspiration (FNA) in diagnosing these tumours. A retrospective analysis of SPTs identified in a tertiary institution EUS database between 2002 and 2009 was performed. Medical records, imaging, EUS features, cytology and histology specimens were reviewed. Patients were followed up until 2009. Seven cases of SPTs were identified out of 2400 EUS performed. All patients were females with a mean age of 41 years (range 22-69). The tumours were solitary with a mean diameter of 2.9 cm (range 2.0-4.3 cm). Five

tumours were located in the body and tail of the pancreas and two in the neck. All lesions were hypoechoic, heterogenous and well circumscribed, with five having a cystic component and two having a calcified rim. FNA using a 22-gauge needle was performed in six cases with no complications. A preoperative diagnosis of SPT based on cytology was obtained in 5/6 cases (83 %). Surgical resection was done in six cases with confirmation of SPT and no metastatic disease. The authors concluded that EUS-guided FNA is a minimally invasive, safe and reliable way of diagnosing SPT by providing characteristic cytological specimens. Definitive preoperative diagnosis leads to targeted and minimally invasive surgical resection [836].

To further delineate the clinicopathological and radiological features of solid pseudopapillary tumor (SPT) of the pancreas and summarize the surgical therapy strategy for this tumor a retrospective review of 18 pathologically confirmed cases of SPT was performed and the clinical and pathological features, radiological findings and surgical interventions were analyzed. The patients included 17 females and 1 male with a median age of 23 years. The median diameter of the lesions was 8.0 cm. Abdominal pain was the predominant complaint (8/18). The rest of the patients were asymptomatic and presented with a pancreatic mass detected incidentally. Radiological study revealed a well-demarcated mass which was composed of a solid-cystic portion. On post-contrast CT, the solid portions could be enhanced whereas the cystic parts remained unenhanced. With the preoperative diagnosis of SPT in 11 patients and pancreatic cyst, benign or malignant pancreatic tumor in the rest, pancreatic tumor resection was successfully completed. Surgical exploration findings, pathological characteristics and good prognosis of the patients with SPT, indicated its low-grade malignant potential. It was concluded that in combination with clinical findings, radiological features of SPT may help to make the correct diagnosis and differentiation from other pancreatic neoplasms. Once diagnosed, given the excellent prognosis and low-grade malignancy, less aggressive surgical resection of the primary lesion is proposed [837].

It was reported 3 cases of a hitherto undescribed ovarian tumor histologically and immunohistochemically identical to pancreatic solid pseudopapillary neoplasms. The patients were aged 17, 21, and 57 years of age. Two tumors involved the left ovary and 1 the right ovary. They ranged from 3 to 25.5 cm and were confined to the ovary. Radiologic investigations did not show an alternative primary site. Grossly the neoplasms were solid and cystic. On microscopic examination they had mostly diffuse and pseudopapillary growth patterns. Other patterns included nested and microcystic, including cysts filled with colloid-like material. The tumor cells were monotonous and the nuclei were round to oval with pale chromatin and occasional longitudinal nuclear grooves. Clear intracytoplasmic vacuoles were noted in 2 cases, and all 3 cases showed eosinophilic globules. Mitoses and atypia were virtually absent. Immunohistochemically, all 3 neoplasms showed intranuclear positivity for β -catenin and loss of E-cadherin reactivity. All 3 tumors were negative for chromogranin, inhibin, and calretinin, although both cases evaluated for thyroglobulin were found negative. One patient has been followed for 6 years and is free of disease. The other 2 cases are recent. The tumors likely to enter into the differential diagnosis include sex-cord stromal tumors, steroid cell tumors, and struma ovarii. The morphologic and immunohistochemical similarity to pancreatic solid pseudopapillary neoplasm facilitates the accurate diagnosis of this rare ovarian neoplasm [838].

To analyze the imaging features of small (≤ 3 cm) solid pseudopapillary tumors (SPTs) seen at multiphasic multidetector computed tomography (CT) in comparison with those of larger SPTs. A retrospective study was approved by the institutional review board, and the requirement for informed consent was waived. CT images of 42 histopathologically proven SPTs in the pancreas were retrospectively reviewed. Two radiologists in consensus analyzed the CT findings for the shape, location, diameter, ratio of solid-to-cystic components, border and margin, enhancement pattern, and enhancement grade of the tumors, as well as the presence of calcification, dilatation of the pancreatic duct, and parenchymal atrophy. Then,

according to the feature analysis results, the reviewers classified all SPTs as typical or atypical; they also subdivided all SPTs into small (≤ 3 cm) and large SPTs (> 3 cm) depending on the tumor size. There were 20 typical SPTs and 22 atypical SPTs. Of the 22 atypical SPTs, 12 (54 %) were 3 cm or smaller in diameter and 10 (45 %) were larger than 3 cm in diameter. Small atypical SPTs usually appeared as solid tumors with a sharp margin and without accompanying pancreatic duct dilatation or parenchymal atrophy. They also showed weak enhancement during the pancreatic phase and a gradually increasing enhancement pattern. All typical SPTs were larger than 3 cm and appeared as well-defined cystic and solid masses with heterogeneous enhancement, while all large atypical SPTs appeared as calcified solid masses or large cystic masses. The imaging features of small SPTs are different from those of large SPTs, and small SPTs frequently appear as purely solid tumors with a sharp margin and gradual enhancement [839].

The mean age of presentation for SPTs is 25 years and the female predominance is more than 20:1. Solid pseudopapillary tumors of the pancreas are unique to the pancreas and pathologically identical in each patient. These tumors have no differentiation, although they do contain pseudopapillary architecture, hyaline globules, and clusters of uniform cells that mimic neuroendocrine tumors. Solid pseudopapillary tumors of the pancreas do not have an epithelial lining (and hence are not true cysts) but are often noted to contain blood, necrotic debris, and clusters of macrophages. They express both progesterone and beta-estrogen receptors, suggesting that their development is hormone linked. Pancreas divisum is also a rare anomaly which develops at 7 weeks of gestation. It was reported a case of a solid pseudopapillary tumor of the pancreas with concomitant pancreas divisum. A 26-year-old woman was diagnosed as having a pancreatic tumor with solid and cystic components in the pancreatic head. Pancreatograms obtained by ERCP and MRCP showed no communication between the ventral and dorsal pancreatic ducts, indicating that pancreas divisum was present. Microscopically, the resected tumor had solid and cystic components. Immunohistochemical study demonstrated that the tumor cells were positive for alpha-1-antitrypsin, vimentin and progesterone receptors but negative for estrogen receptors, NSE, insulin or glucagon. The tumor was diagnosed as a solid pseudopapillary tumor of the pancreas. Although more than 700 cases of solid pseudopapillary tumors of the pancreas have been reported in the English literature, a search of PubMed turned up no reports of concomitant solid pseudopapillary tumor and pancreas divisum [840].

With spindle cells

Solid pseudopapillary tumor of the pancreas is a rare, clinicopathologically distinct neoplasm with a tendency to affect young women and constitute approximately 1 percent of pancreatic neoplasms. The most common localization is the body or the tail (61 %). They appear macroscopically totally or partially cystic in 92 percent of cases. The cut surface is usually gray-white and firm. Microscopically, they have the features of a mixed, solid, papillary cystic tumor. Solid pseudopapillary tumors are classically composed of small and uniform discohesive tumor cells with round nuclei and eosinophilic cytoplasm. Solid pseudopapillary tumors are known to express vimentin, alpha₁-antitrypsin, neuron-specific enolase, progesterone receptors, CD10, CD56, beta-catenin, and E-cadherin. It was now reported an unusual spindle cell variant of SPT, where the tumor was histologically composed of spindle cells. The tumor displayed a predominantly solid growth pattern and lacked the characteristic pseudopapillary pattern of classic SPT. The patient was a 44-year-old woman who presented with upper abdominal pain for 6 months, which was exacerbated by eating. Clinical examination revealed no detectable abnormality. On computed tomography, a circumscribed large mass was found arising from the body and the tail of the pancreas and compressing the splenic vein. Intraoperatively, there was a large tumor expanding and replacing the body and the tail of the pancreas. The patient underwent distal pancreatectomy. The tumor was a well-circumscribed mass in the body and the tail of the pancreas that measured 9 × 8.5 × 7 cm. The cut surface of the mass was solid fleshy brown with small areas of hemorrhage.

Microscopically, the tumor was composed of spindle cells arranged in small packets and sheets with focal areas showing a storiform pattern. The tumor cells were spindle shaped with elongated nuclei and eosinophilic cytoplasm. There was mild nuclear pleomorphism. The mitotic index was 2 mitoses per 50 high-power fields. There were foci of cellular discohesion and small spaces but no typical pseudopapillary pattern. The tumor was richly vascular. No lymphovascular or perineural invasion was seen. The tumor was completely excised. On immunostaining, the cells expressed CD56, PgR, CD10, and alpha₁-antitrypsin and were negative for chromogranin, CD117, cytokeratins, MelanA, calponin, caldesmon, desmin, CD31, and CD34. The tumor showed nuclear localization of E-cadherin in all tumor cells with complete absence of membranous and cytoplasmic immunoreactivity. Intense beta-catenin immunoreactivity was found in the cytoplasm and the nuclei of most tumor cells, with no membranous reactivity. The immunophenotype was typically that of SPT. Solid pseudopapillary tumors usually present as large, hemorrhagic masses that exhibit prominent cystic change. The present case showed no cystic change on radiological or gross examination but appeared as a solid mass. Solid pseudopapillary tumors with no cystic component have been reported. Histologically, the appearance of SPTs is quite characteristic if not diagnostic, in most cases. In the reported case, the tumor was composed of spindle cells, causing a diagnostic difficulty and bringing other spindle cell lesions of the pancreas into the differential diagnosis. Other spindle cell lesions of the pancreas include leiomyosarcoma, gastrointestinal stromal tumor, solitary fibrous tumor, schwannoma and neurofibroma, mesenchymal chondrosarcoma, malignant fibrous histiocytoma, sarcomatoid carcinoma, inflammatory myofibroblastic tumor, malignant islet cell tumor with sarcomatous differentiation, malignant peripheral nerve sheath tumor, spindle cell hemangioendothelioma, spindle cell stromal tumor of the pancreas, rhabdomyosarcoma, Kaposi sarcoma, and metastatic tumors as dermatofibrosarcoma protuberans. The biological behavior and prognosis of SPT are different from other spindle cell lesions of the pancreas, most of which are aggressive malignant tumors, whereas most SPTs are indolent neoplasms with low malignant potential, and surgical resection may provide more than 95 percent cure rate, hence, distinction is important in deciding patient management. In the presented case, 5 years after resection, the patient remained disease-free, which is well in keeping with the biological behavior of most classic SPTs [841].

Acinar cell adenocarcinoma

Acinar cell carcinoma (ACC) of the pancreas is very rare and usually grows expansively. Recently, a variant of ACC with predominant growth in the pancreatic ducts has been proposed, and is speculated to have potentially less aggressive behavior. The aim of one study was to investigate how the pancreatic duct system is related to the growth and extension of ACC. It was reviewed the detailed gross and histologic features of 13 cases of ACC, of which 7 (54 %) showed intraductal polypoid growth (IPG) of the tumor in the large pancreatic ducts with a mean IPG length of 25 mm. Tumors with IPG were found to spread characteristically along the pancreatic ducts as extending polypoid projections, filling the ducts and destroying the duct walls, although tumors did not tend to extend beyond the pancreatic parenchyma. Comparison of the clinicopathologic characteristics showed that ACC with IPG had less infiltrative features including lymphatic, venous, and neural invasion, formation of tumor thrombus in the portal vein, nodal metastasis, and invasion beyond the pancreas to the surrounding organs; death in only one case (14 %) of ACC with IPG was the result of ACC itself. In contrast, ACC without IPG frequently showed more infiltrative growth, and was the cause of death in 50 percent of patients with this type of tumor. Intraductal dissemination of ACC in pancreatic ducts was proven in one case of ACC with IPG. These findings suggest that a significant proportion of ACC shows IPG, which is potentially linked to less aggressive clinicopathologic characteristics [842].

A 55-year-old man underwent a pylorus-preserving pancreatoduodenectomy in 2006 because of acinar cell carcinoma of the head of the pancreas. Since abdominal CT revealed multiple liver metastases, it was started systemic chemotherapy with gemcitabine (1,400 mg/body, day 1, 8, 15/q4w). At the beginning of this treatment, it seemed to be a stable disease, but CT revealed tumor progression after five months. Despite the change to oral chemotherapy with S-1 (100 mg/body, day 1-14/q3w), tumors were markedly enlarged. Therefore, we selected combination chemotherapy with oral S-1 and hepatic arterial infusion of CDDP (50 mg/body) as third-line. After 6 months of treatment, abdominal CT revealed marked shrinkage of tumors, accompanied by a decrease in AFP level. Though the patient died of hepatic failure in July 2009 (33 months after recurrence), he spent most of his time at home and worked as usual [843].

Adenosquamous carcinoma

Among exocrine pancreatic tumors, adenosquamous carcinoma (ASC) is a rare, aggressive subtype with a worse prognosis and a higher potential for metastases compared to its more conventional glandular counterpart, adenocarcinoma. The disease distribution shows an approximately 1:1 male/female ratio and a median survival of circa five months. Although such features as central necrosis and hypervascularity are suggestive of pancreatic ASC, more research is necessary to identify other, more specific markers for this tumor subtype. Humoral hypercalcemia of malignancy has also been described with ASC of the pancreas, likely as a result of PTHrP production by the squamous component of the tumor. Similar to the therapeutics of pancreatic adenocarcinoma, adjuvant chemotherapy or chemoradiotherapy is currently indicated for resectable ASC of the pancreas, while gemcitabine or gemcitabine combinations are used for a more advanced disease. Both pathologic and molecular features of pancreatic ASC characterize it as a distinct subtype of pancreatic cancer. As a result, its molecular and genetic makeup could be exploited for both diagnostic and therapeutic quests in the future [844].

Pancreatic small cell carcinoma

It was presented one case of a pancreatic small-cell carcinoma presenting as acute pancreatitis [845].

Intraductal oncocytic papillary neoplasm

An intraductal oncocytic papillary neoplasm is a rare pancreatic tumor with the potential of developing invasive carcinoma. Its differentiation from other cystic-like neoplasms of the pancreas, such as intraductal papillary mucinous neoplasms, is a challenge for pancreatic imaging. It was presented a case of a 76-year-old male with painless jaundice caused by an intraductal oncocytic papillary neoplasm of the pancreas. Computed tomography, magnetic resonance including diffusion-weighted imaging, and ¹⁸F-fluorodeoxyglucose positron emission tomography were performed. An intraductal oncocytic papillary neoplasm of the pancreas appears as a cystic tumor communicating with the dilated pancreatic duct featuring intraductal tumor nodules. Intraductal oncocytic papillary neoplasms show a high ¹⁸F-fluorodeoxyglucose-uptake in positron emission tomography and low diffusion values in diffusion-weighted imaging including apparent diffusion coefficient maps which may be a valuable attribute in distinguishing these rare lesions from intraductal papillary mucinous neoplasms [846].

Serous microcystic adenoma

Serous microcystic adenoma (SMCA) is a rare pancreatic tumor with a striking predilection for elderly females and a rather unique morphology. Classically, the tumor is riddled with innumerable small cysts around a stellate scar. The quintessential histological features are closely placed small cysts lined by glycogen rich cuboidal epithelium. In view of its excellent prognostic outcome, this tumor needs to be accurately diagnosed. One report documented a case of SMCA occurring in a 60-year-old female [847].

Mixed acinar-ductal carcinoma

Pancreatic acinar cell carcinomas (ACCs) are clinically and pathologically distinct from pancreatic ductal adenocarcinomas (PDAs). Whereas endocrine differentiation has been well shown in ACCs, significant ductal components are rare. One paper reviewed the clinicopathologic features of a series of ACCs with prominent ductal differentiation. Eleven cases were identified (10 men and 1 woman; age range 52 to 79 years). Four patients presented with jaundice. At last follow-up, 7 patients died of disease and 2 others had recurrences. Tumors measured between 2 and 5.5 cm and were ill-defined, nodular, and multilobulated. Ten were located in the head of the pancreas. All but 2 exhibited extrapancreatic invasion. All cases showed significant evidence of both acinar and ductal differentiation, estimated to be at least 25 percent of the neoplastic cells, and 3 cases in addition had endocrine differentiation in more than 25 percent of cells. Five cases were predominately acinar with intracellular and sometimes extracellular mucin ("mucinous acinar cell carcinoma" pattern). Six cases seemed more mixed with areas recapitulating typical PDAs whereas the other portions of the tumors seemed akin to typical acinar cell carcinomas ("combined acinar and ductal" pattern). IHC positive staining results were as: trypsin (92 %), chymotrypsin (92 %), monoclonal carcinoembryonic antigen (100 %), CK19 (100 %), B72.3 (73 %), CA19.9 (73 %), CD56 (18 %), synaptophysin (36 %), and chromogranin (36 %). One case showed p53 over-expression and none showed DPC4/Smad4 loss. Two cases had KRAS2 mutations. Despite the early embryologic divergence of acinar and ductal cell lineages, rare pancreatic tumors have both acinar and ductal differentiation, usually predominantly the former. The clinical course is highly aggressive [848].

Mixed acinar-endocrine carcinoma

A 75-year-old asymptomatic man, in whom a tumor mass in the pancreatic tail had been found 6 months earlier had a CT that revealed a mass 7 cm in diameter, and an enhancement with contrast medium was observed at the periphery and partially inside the mass, but not in most parts of the tumor. Endoscopic retrograde cholangiopancreatography showed a filling defect in the main pancreatic duct. A distal pancreatectomy was performed because of the possibility of a malignant tumor. The tumor consisted of a lobular invasive growth component and a component with intraductal growth into the main pancreatic duct, and histologically the tumor cells had solid acinar to partially trabecular/tubular patterns. Trypsin (an acinic cell marker) expression was widely observed, followed by the expression of chromogranin A (an endocrine cell marker) in about 30 percent of the tumor cells. The tumor was diagnosed as mixed acinar-endocrine carcinoma according to the WHO classification [849].

Adenosquamous carcinoma

Pancreatic adenosquamous carcinoma is a rare morphological variant of pancreatic adenocarcinoma with an especially poor prognosis. The purpose of one study was to identify clinicopathologic features associated with prognosis, assess whether the percentage of squamous differentiation in pancreatic adenosquamous carcinoma is associated with an inferior prognosis, and examine the impact of adjuvant chemoradiation therapy on overall survival. Forty-five (1.2 %) of 3651 patients who underwent pancreatic resection at the Johns Hopkins Hospital, Baltimore, MD, between 1986 and 2007 were identified with adenocarcinoma of the pancreas with any squamous differentiation. All pathologic specimens were re-reviewed. Statistical analyses were performed on the 38 patients amenable to adjuvant chemoradiation therapy for whom clinical outcome data could be obtained. Median age was 68 years (61 % male). Sixty-one percent underwent pancreato-duodenectomy. Median tumor size was 5.0 cm. Seventy-six percent of carcinomas were node positive, 37 percent were margin-positive resections, and 68 percent had 30 percent or more squamous differentiation. Median overall survival of the pancreatic adenosquamous carcinoma cohort was 11 months (range, 2-141 months; 95 % confidence interval, 8-13 months). Adjuvant chemoradiation therapy was associated with significantly superior overall survival in patients with pancreatic adeno-squamous carcinoma. Adjuvant chemoradiation therapy was associated with significantly improved survival in patients with tumors 3 cm or larger and vascular or perineural invasion. The proportion of squamous differentiation was not associated with median overall survival. Survival after pancreatic resection of pancreatic adenosquamous carcinoma is poor. Treatment with adjuvant chemoradiation therapy is associated with improved survival. The proportion of squamous differentiation in resected pancreatic adenosquamous carcinoma specimens does not appear to impact overall survival [850].

Schwannoma

It was reported the imaging features of pancreatic schwannomas, a rare benign type of pancreatic tumor. A 66-year-old woman was admitted to hospital with a pancreatic tumor indicated in medical examinations. Computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) revealed a solid and cystic tumor, 3 cm in diameter, within the body of the pancreas. Contrast-enhanced CT, MRI and ultrasonography showed partial enhancement in the solid component. Endoscopic retrograde cholangiopancreatography (ERCP) and angiography showed no abnormal findings. A distal pancreatectomy together with a splenectomy and lymph node dissection were performed with a tentative diagnosis of mucinous cystic neoplasm of the pancreas. The cut surface of the resected pancreas showed a well-demarcated, pale yellow, solid tumor within the pancreas parenchyma. Histopathological examination of the tumor revealed proliferation of the spindle cells showing interlacing and palisading patterns. Immunohistochemically, these spindle cells were positive for S-100 protein and vimentin, and negative for alpha-smooth muscle actin, CD34, and cytokeratin. Thus the tumor was diagnosed as a pancreatic schwannoma. It was concluded that CT and US can detect pancreatic schwannomas as solid and cystic masses, and MRI shows a relatively characteristic feature. Imaging procedures such as CT, MRI and US are able to differentiate a pancreatic tumor, such as a pancreatic schwannoma [851].

Pancreatic schwannoma is a very uncommon tumor of the pancreas, with only 27 cases reported. Most pancreatic schwannomas are benign, with only four malignant tumors reported. It was described a case of giant malignant schwannoma of the pancreatic body and tail, which involved the transverse colon. The tumor was treated successfully with en bloc distal splenopancreatectomy and colon resection. This is believed to be the first reported radical operation for malignant schwannoma of the pancreatic body, with infiltration of the

transverse colon, with excellent long-term results. The patient is alive and well 28 months after the operation. The authors conclude that pancreatic schwannomas should be considered in the differential diagnosis of cystic neoplasms of the pancreas, although the diagnosis can only be confirmed by microscopic examination. In the case of the benign tumors, local excision is adequate, but in the case of malignant schwannoma, oncological standards must be fulfilled [852].

Pancreatic lipomas

Compared with pancreatic ductal adenocarcinoma, mesenchymal tumors occupy only 1-2 percent of all pancreatic neoplasms. Lipomas are a rare variant of mesenchymal tumors of the pancreas. In one study, it was reviewed the literatures on pancreatic lipoma and gathered the data of these cases, and clinical analysis was made to investigate the clinical manifestation, the diagnosis, and the treatment measures. A systematic literature search was performed using MEDLINE, EMBASE, and the Cochrane databases, with the last search on March 19, 2009. Finally, 45 cases were extracted from 21 literatures, which included three cases published in a Chinese journal. The genders of 44 patients in these 45 cases were identified, which include 19 males and 25 females. The age ranged from 11 months to 83 years old; the mean (SD) age was 62 (15) years. Only 7 patients in these 45 cases had an upper abdominal pain; one patient was admitted and examined because of acute pancreatitis. Renal colic was diagnosed in one patient; the other patients underwent image examinations for several clinical disorders, none of which were related to pancreatic problems. The locations of the pancreatic lipomas are as follows: head (n=16), uncinata process (n=8), body (n=6), body-tail junction (n=2), and tail (n=13). All cases were single lesions, the largest mean (SD) diameter of the lesions was 29 (47) mm, ranging from 4 to 300 mm. These 45 cases were diagnosed by computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), or a combination of these. Seven patients underwent operations, and the pathological result confirmed the diagnosis. Two patients received EUS-fine needle aspiration (FNA); they also had the pathological results. The follow-up process was mentioned in only 11 cases. The follow-up of these 11 patients were between 3 and 72 months (mean, 28 months), with no significant change of the pancreatic lipoma. Until now, the etiopathogenesis is still not very clear. It has been presumed that they may originate from the plane of fusion of the dorsal and the ventral pancreatic buds during the early embryonic development stage. The presumption is that lipomas located in the head or the uncinata process of the pancreas probably generate from the trapped retroperitoneal or mesenteric fat when the ventral and dorsal integrate. This theory may be helpful to explain the genesis of lipoma located in the head or the uncinata process of the pancreas, but as mentioned lesions located in the head and the uncinata process of the pancreas only accounted for 53 percent of the total cases. How does the lesion in the body and the tail arise? This still remains unclear. For the pathological feature, like the lipomas in other locations, pancreatic lipomas consist of lobules of mature adipose cells and have a clear margin from the surrounding pancreatic tissue by a thin fibrous capsule. Thin connective tissue septa may be seen in the mass. The thin fibrous capsule (<2 mm) is very meaningful in differential diagnosis. According to the statistical results presented, only 18 percent of the patients (8/45) have symptoms that are relevant to pancreatic lipoma. A benign pathological feature, 47 percent of the lesion located in the body and tail, and most tumor sizes are below 3 cm (71 %). All these factors attribute to this phenomenon. However, some symptoms may arise when the tumor grows to a certain extent, such as abdominal pain and mass, jaundice, and sinistral portal hypertension. Because the clinical progress of these lesions seems to be silent, most patients were diagnosed by the imaging examination incidentally. Therefore, it was presumed that the incidence rate of pancreatic lipoma may be higher than what we believed. There were 11 cases reported before the year 2000. However, 34 cases have been found since 2000. This indicates that a lot of cases have missing

diagnoses. Based on the review of the relevant literatures, it was found that almost all pancreatic lipoma cases were diagnosed by imaging methods, some of which were confirmed by the pathological examination. Computed tomography is the most widely used radiological method to diagnose pancreatic lipoma according to the review result. Forty-three (96 %) of 45 patients underwent CT examination as the basic/unique method to diagnose this disease. The diagnostic criteria for lipomas were as follows: solid, homogeneous, clear margin without any continuity with the peripancreatic adipose tissue, no signs of invasion of adjacent organs, well-complete thin capsule, CT density value between -30 to -150 Hounsfield units, and with no contrast enhancement. What must be emphasized is that the tumor size and the CT density value are highly variable, and homogeneous fatty attenuation, lack of contrast enhancement, and clear margin are the most important key points to the diagnosis of pancreatic lipoma. Magnetic resonance imaging is another radiological method used to diagnose pancreatic lipoma. The characteristic features that show on CT imaging can also be seen in MRI. Three patients underwent positron emission tomographic (PET) examination for some reasons in the reviewed literatures. There is no uptake of 2-deoxy-2-[¹⁸F]fluoro-d-glucose in 2 patients.¹⁵ However, in 1 patient, the PET scan showed a small focus of increased uptake in the region of the pancreas; the following CT scan excluded the metastasis and confirmed the diagnosis of pancreatic lipoma. The author revealed that this phenomenon may relate to an abnormally vascular lipoma or the presence of brown fat. This may give some helpful information in treating the pancreatic false-positive PET results. For differential diagnosis, focal fatty infiltration, one of the most common histological changes observed in the pancreas is the most important process. Lack of clear margin from the adjacent peripancreatic fat and absence of the thin collagen capsule are the most important features to distinguish with pancreatic lipoma. Histopathologically, foci or nests of atrophic pancreatic parenchyma are the characteristic changes in the focal fatty infiltration, whereas thin septa usually appeared in pancreatic lipoma. A thin section-reconstructed image may be helpful to demonstrate the continuity of the fatty zone in the pancreas with the peripancreatic adipose tissue. Primary sarcomas of the pancreas are very rare, accounting for a small fraction of pancreatic malignancies. It is hard to distinguish a lipoma and a well-differentiated liposarcoma because of the histologic and radiographic similarities between these two lesions. Its homogeneous CT fatty attenuation is the most reliable method to distinguish a lipoma from a well-differentiated liposarcoma. Pancreatic teratoma is very rare, and only 21 cases were reported in the literatures. Teratoma are neoplasms of germ cell origin that are able to generate tissues from all the three germ layers. The relative proportions of various tissues determine the CT appearance; pancreatic lipomas have a uniform CT density value identical to that of a mature adipose tissue, whereas teratomas contain cystic and solid elements and are not within the range of fat. This is very meaningful in distinguishing with lipoma. What is more important is that it is harder to distinguish teratoma from pancreatic cystic lesions, such as cystadenoma, and solid pseudopapillary tumor of the pancreas [853].

The purpose of one study was to describe the computed tomography (CT) findings of pancreatic lipomas of 9 cases, with emphasis to diagnostic challenges. Clinical data and CT features of these 9 cases were retrospectively analysed. The patient population included 5 men and 4 women, aged 42-81 years (mean age 66 years). The patients were followed up for at least 2 years with control CTs. In all 9 cases, a well-bordered nodular fat density lesion was incidentally detected in the pancreas. Four of the lesions had a lobulated contour, and 2 of them had septations. Two of the lipomas were located in the head, 3 in the neck, 3 in the corpus, and 1 in the tail. The CT densitometric values were between -90 and -120 HU, with a mean value of -106 HU. No pancreatic or biliary dilatation or compression to the adjacent structures was seen. All the cases had control CTs, and the lipomas remained unchanged during the follow-up period. Histopathologic confirmation of the diagnosis was not planned for the cases. It was concluded that lipomas are rarely encountered in the pancreas. They often are diagnosed coincidentally as small, well-circumscribed, encapsulated, homogeneous, mature adipose masses on imaging studies. Imaging follow-up strategy or histopathologic confirmation is not necessary in asymptomatic patients [854].

Lipomatous pseudohypertrophy

Lipomatous pseudohypertrophy of the pancreas: a clinicopathologically distinct entity. Owing to the challenges in obtaining pancreatic biopsies, pancreatic resection for presumed malignancy is often performed without histological confirmation. As a result, benign lesions are sometimes surgically removed. One such condition, which is poorly defined in the literature, is referred to as lipomatous pseudohypertrophy of the pancreas. Five such cases were analyzed. Four patients underwent surgical resection, 3 of which were diagnosed preoperatively by radiology as having ductal adenocarcinoma. The fourth case was correctly interpreted by magnetic resonance imaging, but the patient underwent resection because of the intractable pain due to pancreatitis. The fifth patient has been placed on watchful waiting. Two tumors were in the pancreatic head, one in the tail, one in the uncinata process, and one demonstrated diffuse involvement. Microscopically, they were characterized as having normal lipocytes without lipoblasts or inflammation. Within the adipose tissue, scattered microscopic foci of pancreatic parenchyma could be seen. It was concluded that lipomatous pseudohypertrophy of the pancreas is a distinct entity characterized by localized/diffuse replacement of pancreatic parenchyma with mature adipose tissue. It forms a pseudotumor that may be difficult to distinguish clinically from pancreatic adenocarcinoma. This entity should be considered when evaluating patients with a new diagnosis of a hypodense pancreatic neoplasm on imaging [855].

Pancreatoblastoma

Pancreatoblastoma (PB) is extremely rare. An 11-year-old boy, who had excision of dilated common bile duct with hepaticoduodenostomy when 9 years old was referred for further management of abdominal pain and steatorrhea. Imaging studies showed a solid 4 cm tumor in the head of the pancreas and two lesions in the liver. Needle biopsies diagnosed PB with liver metastases. After five courses of chemotherapy, the primary tumor was completely resected with pancreaticoduodenectomy (PD) and Child's pancreaticobiliary tract reconstruction. The liver metastases were resected. Postoperative recovery was uneventful [856].

Although pancreatoblastoma (PB) is an extremely rare tumor, it is the most common pancreatic tumor in children. It was reported two cases of PB. One was a 3.5-year-old boy who presented with abdominal pain. Physical examination demonstrated abdominal masses. Multiple pancreatic and hepatic masses were noted by magnetic resonance imaging. He underwent surgical resection but tumor could not be removed completely, which was confirmed by the pathology. He received chemotherapy consisting of cisplatin and doxorubicin after the surgery but the tumor progressed rapidly. He died of progressive disease and sepsis. The other case was a 4-year-old boy presented with abdominal pain. Computed tomography showed pancreatic tumor. He underwent surgical resection and pathology showed PB. He received chemotherapy after complete tumor resection. He is disease free till now. Complete tumor resection is the major difference of these 2 patients and is the most important factor affecting the outcome [857].

Other pancreatic tumors in children

Malignant pancreatic tumors are exceedingly rare in pediatric age and their clinical features and treatment usually go unappreciated by most pediatric oncologists and surgeons. From 2000 to 2009, 21 patients <18 years old with pancreatic tumors were prospectively registered in the Italian cooperative TREP project dedicated to very rare pediatric tumors. Tumor types were 4 pancreatoblastomas, 2 pancreatic carcinomas, 3 neoplasms of the endocrine

pancreas, and 12 solid pseudopapillary tumors. Three of the four patients with pancreatoblastoma had advanced disease at diagnosis and were given chemotherapy; at the time of this report, three patients were alive in first remission, while one died due to treatment toxicity. Both the cases of pancreatic carcinoma had the acinar cell subtype and successfully underwent pancreaticoduodenectomy with complete tumor resection, remaining without evidence of disease at the time of this analysis. The histological diagnoses of the three endocrine tumors were a malignant islet cell tumor, a gastrinoma, and a well-differentiated tumor. All 12 patients with solid pseudopapillary tumors underwent complete tumor resection and were given no adjuvant treatment; 11 were alive in first remission, while one experienced a local and distant relapse 5 years after diagnosis. It was concluded that surgery remains the keystone of treatment for pancreatic tumors in pediatric age as in adults. The TREP project shows that prospective cooperative studies are feasible even for such very rare tumors as these and may serve as a model for developing international cooperative schemes [858].

Malignant mesothelioma

Malignant mesothelioma usually presents with diffuse involvement of the pleura or peritoneum. Circumscribed or localized malignant mesothelioma has been described in these locations, as well as the viscera, in which case it may cause diagnostic confusion with other, more common entities. Herein, it was described the first well-documented case of primary intrapancreatic malignant mesothelioma in the English literature. The patient was an otherwise healthy 39-year-old woman who presented with a symptomatic mass in the head of the pancreas that was completely resected via pancreaticoduodenectomy. The tumor was composed of cysts, papillae, and tubules lined by cells with abundant eosinophilic cytoplasm and immunohistochemically expressed CA-125, calretinin, and D2-40. Follow-up revealed no evidence of residual or recurrent disease 32 months after surgery. This report also describes the clinical and pathologic characteristics of an intrapancreatic mesothelioma and provides a review of the literature regarding entities that may be considered in the differential diagnosis of this tumor [859].

Pancreatic leiomyosarcomas

Primary pancreatic leiomyosarcomas are rare lesions and not well described, yet they are the most common primary pancreatic sarcoma. English-language medical literature reports 29 cases as single cases or small series. A systematized nomenclature of medicine (SNOMED) search of Mayo Clinic surgical pathology files from 1994 to 2006 identified 22 primary pancreatic leiomyosarcomas. Nine patients with pancreatic leiomyosarcoma were diagnosed and treated at our institution (5 males and 4 females; mean age at diagnosis, 63 y; range, 39 to 87 y) are described, with a literature review. In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) was conducted in all cases to exclude EBV-associated smooth muscle tumor (EBV-SMT). Seven of the 9 patients presented with abdominal pain, weight loss, and jaundice. Seven tumors (mean, 10.7 cm; range, 1.0 to 30 cm) were located in the pancreatic head and 2 in the tail. Histologic findings of primary pancreatic leiomyosarcomas (7 spindle and 2 epithelioid) were similar to leiomyosarcomas of other sites. All tumors stained positive for smooth muscle actin and desmin and negative for KIT. No case showed EBER positivity. Pancreaticoduodenectomy was done in 4 patients; 3 patients had palliative procedures, and 2 had biopsy only. No lymph node metastasis was identified in 4 resected tumors, but liver metastases were present in 4 patients. All patients died; 5 deaths were known to be disease related (overall mean survival, 31 months; range, 5 to 98 mo). Historical cases showed similar clinicopathologic findings. These pancreatic leiomyosarcoma lesions have the same morphologic features as their counterparts of other sites. EBER testing should be conducted – especially for pediatric patients – to rule out EBV-

SMT. The tumor is likely to metastasize to liver but not regional lymph nodes. Extensive surgical resection should be advocated, even when morphologic results show a low-grade lesion [860].

Pancreatic mesenchymal chondrosarcoma

Extraskelatal chondrosarcomas are rare and there is only one reported case of primary pancreatic chondrosarcoma. It was reported a case of a 34-year-old woman with a 6-month history of abdominal pain and distention. Radiological studies indicated a mass in the pancreas, and exploratory laparotomy revealed a tumour of the pancreas extending to the hepatic vessels and hepatoduodenal ligament. The mass was completely excised, and the histopathological diagnosis was primary mesenchymal pancreatic chondrosarcoma. The tumor recurred at follow-up 52 months postoperatively [861].

Multiple myeloma

A pancreatic head mass of unusual etiology was discussed: multiple myeloma diagnosed by endoscopic ultrasound-guided fine needle aspiration [862].

Acute lymphoblastic leukaemia

A 39-year-old man presented with a 4 month history of weight loss and a 6 week history of upper abdominal pain radiating to the back with nausea and vomiting. Liver function tests showed an obstructive picture, full blood count was normal and on computerised tomography there was diffuse enlargement of the pancreas, with dilatation of the common bile duct and intra hepatic biliary radicles. Four weeks after presenting, the white cell count became elevated with blasts on the blood film and bone marrow biopsy revealed a precursor B cell acute lymphoblastic leukaemia. After induction chemotherapy his jaundice resolved, the pancreatic mass reduced in size and he is now in a complete remission. This means that acute lymphoblastic leukaemia may mimic common causes of a pancreatic mass such as adenocarcinoma and should be considered as part of the differential diagnosis when atypical features are present [863].

Pancreatic lymphoma

To investigate the clinical feature and treatment strategy of primary pancreatic lymphoma 39 cases of primary pancreatic lymphoma reported in China were reviewed retrospectively with their clinical characters, treatment, and outcome, as well as a literature review of worldwide reports. The major clinical presentations included discomfort or pain in the upper abdomen and jaundice without specificity. Only 2 cases were identified correctly by computed tomography, and 5 cases obtained a positive finding in a biopsy before operation. Thirty-two patients accepted operation; 13 pancreatoduodenectomy and 6 distal pancreatectomy were performed. Thirty-one patients accepted postoperative chemotherapy. Until now, 26 patients are still alive at a range of 3 to 72 months; 5 patients died at 5 to 24 months after operation. The literature review revealed 85 additional cases of pancreatic lymphoma in English reports. Their diagnosis and treatment methods varied. It was concluded that primary pancreatic lymphoma was misdiagnosed as pancreatic adenocarcinoma frequently. Fine needle aspiration biopsy is the most valuable method in preoperative diagnosis. The value of surgery and radiotherapy remains controversial; an operation combining chemotherapy

seems to be an appropriate method of treatment for a patient in whom malignancy cannot be ruled out [864].

The aim of one study was to report a single center experience of primary pancreatic lymphoma (PPL) in Korea. It was analyzed the clinicopathological data from four PPL patients (three male, median age 36 years) diagnosed from 1997 to 2007. The diagnoses were: diffuse large B cell lymphoma (n=2), Ki-1 (+) anaplastic large cell lymphoma (n=1), and Burkitt lymphoma (n=1). Presenting symptoms and signs were: abdominal pain (n=4), pancreatitis (n=2), weight loss (n=2) and abdominal mass (n=1). No patient underwent surgery. The Ann Arbor stages of the patients were: IEA (n=1), IIEA (n=1), and IVEB (n=2). Two patients underwent treatment. The stage IEA patient underwent chemotherapy and radiation therapy that resulted in a complete remission. The stage IVEB patient who underwent chemotherapy relapsed. This patient underwent subsequent peripheral blood stem cell transplantation and is alive at 30 months. Two patients (stages IVEB and IIEA) without treatment died at 1 and 7 months, respectively. For PPL patients, chemotherapy-based treatment, and addition of radiation therapy, if possible, may offer good prognosis [865].

Cytology

The diagnosis subtyping of lymphoma on specimens collected by endoscopic ultrasound fine-needle aspiration (EUS-FNA) can be extremely difficult. When a cytopathologist is available for the on-site evaluation, the diagnosis may be achieved by applying flow cytometric techniques. We describe our experience with immunocytochemistry (ICC) and molecular biology studies applied on EUS-FNA specimens processed with a liquid-based cytologic (LBC) preparation for the diagnosis of primary pancreatic lymphoma (PPL). Three patients with a pancreatic mass underwent EUS-FNA. The collected specimens were processed with the ThinPrep method for the cytologic diagnosis and eventual additional investigations. A morphologic picture consistent with PPL was found on the LBC specimens of the 3 patients. Subsequent ICC and molecular biology studies for immunoglobulin heavy chain gene rearrangement established the diagnosis of pancreatic large B-cell non-Hodgkin lymphoma in 2 patients and a non-Hodgkin lymphoma with plasmoblastic/immunoblastic differentiation in the remaining one. It was concluded that an LBC preparation can be used to diagnose and subtype PPL by applying ICC and molecular biology techniques to specimens collected with EUS-FNA. This method can be an additional processing method for EUS-FNA specimens in centers where on-site cytopathologist expertise is not available [866].

Non-Hodgkin's lymphoma

The involvement of certain organs such as the adrenal gland and ovaries is rare in non-Hodgkin's lymphoma (NHL). There are few studies comparing clinical features and prognosis based on the extranodal organ involved. It was selected patients presenting with predominantly extranodal involvement among patients diagnosed with NHL from 1998 to 2009. Forty-eight patients with NHL involving rare extranodal sites were analyzed. The extranodal sites were as follows: adrenal gland (n=14), ovary (n=13), pancreas (n=11), uterus (n=4), esophagus (n=4) and prostate (n=2). Diffuse large B-cell lymphoma (DLBCL) was the most common (n=39), and the median overall survival (OS) was 17 months. There was no significant difference in OS according to the involved sites. Rituximab plus CHOP failed to provide an additive survival benefit over CHOP alone in 39 DLBCL patients. The OS of DLBCL in rare extranodal sites was worse than that in common sites when compared based on tumor stage. It was concluded that NHL involving rare extranodal sites had a poor prognosis, and the impact of rituximab on survival was negligible. Thus, more intensive therapeutic strategies should be considered for NHL involving rare extranodal sites [867].

Burkitt lymphoma

A 10-year-old boy was referred to our clinic for tonsillectomy and was found to have a large mass within his oropharynx. Intraoperative biopsies confirmed Burkitt lymphoma. Further imaging and biopsy revealed pancreatic involvement. He was treated with multiagent chemotherapy. He remains disease-free 6 years later. Review of the literature demonstrates other cases of non-Hodgkin lymphoma with pancreatic involvement with good outcomes. Pancreatic involvement is a relatively rare occurrence in childhood lymphoma [868].

Metastases to pancreas

Tumors metastasizing to the pancreas are rare, and published series are limited by few patients treated for extended periods of time. Renal cell cancer (RCC) is the most common primary tumor metastasizing to the pancreas. Our aim was to describe the clinicopathologic characteristics and patient outcomes in a modern series of patients who underwent metastasectomy, with an emphasis on RCC. It was made a retrospective review of all pancreatic resections between 1993 and 2009. It was identified 40 patients with a median age of 62 years; 55 percent were female. Patients most commonly presented with abdominal pain (48 %). Operations performed included 10 pancreaticoduodenectomies, 1 middle, 23 distal, 3 total pancreatectomies, and 3 enucleations. Primary cancers were RCC (n=20), ovarian (n=6), sarcoma (n=3), colon (n=3), melanoma (n=2), and others (n=6). Median survival for all patients after metastasectomy was 4 years. Median survival after metastasectomy for RCC was 9 years, and the 5-year actuarial survival was 61 percent. For RCCs, pancreas was the first site of an extrarenal recurrence in 85 percent and was synchronous with the primary in 5 percent of patients. There was no survival difference if the time interval to metastasis was shorter than the median (9 years), if tumor nodules were multiple or bigger than the median (3 cm), or if the pancreas was not the first site of metastases. It was concluded that an aggressive approach to lesions metastatic to the pancreas is often warranted if the patient can be rendered free of disease. Although patients with RCC can experience long-term survival after metastasectomy, survival is less favorable for other primary tumors [869].

It was also reported an ocular melanoma metastatic to the pancreas after a 28-year disease-free interval [870].

Cancer metastatic to the pancreas from other primary sites is uncommon, and it has been treated with an aggressive surgical approach in fit patients when the primary tumor is controlled and the pancreas is the only site of metastatic disease. The value of pancreatic resection in this setting is unclear. The purpose of one study was to review cases of cancer metastatic to the pancreas. It was reviewed our experience with cancer metastatic to the pancreas and the literature regarding resection of pancreatic metastases. Patient and tumor characteristics were summarized using descriptive statistics. A total of 220 patients with pancreatic metastasis were analyzed. Three patients were selected from a personal experience, and 217 were selected from a literature review. In the 127 patients whose symptoms were recorded at the time of presentation, the most common presenting symptoms were jaundice (n=32, 25 %) and abdominal pain (n=25, 20 %). In the 189 patients for whom the location of the metastasis in the pancreas was revealed, the most common location was the head of the pancreas (n=79, 42 %). The primary tumor site was most commonly kidney (n=155, 71 %). Surgical resection was attempted in 177 of 220 patients; 135 patients suffering from renal cell carcinoma (RCC) metastasis also underwent pancreatic resection. In the latter group, a median survival of 70 months was seen, as well as 78% percent and 65 percent 2- and 5-year survival rates, respectively. It was concluded that survival after resection of RCC with isolated metastasis to the pancreas is favorable.

However, a more detailed analysis considering outcomes without surgery for each primary tumor site is needed before the value of this aggressive surgical approach can be completely assessed in the general occurrence of pancreatic metastasis [871].

Pancreatic metastases are rare. Data from patients with pancreatic metastases observed in from 2003 to 2008 were retrospectively analyzed. In addition, the recent English medical literature was reviewed regarding series of patients with pancreatic secondary tumors. Data from 234 patients including 9 consecutive patients observed were retrieved. Metastasis from renal cell carcinoma accounted for 68 percent of all cases. Factors predictive of worse survival, as determined by multivariate analysis, were symptoms at diagnosis, synchronous tumors, radical-intent surgery not performed, and pathologic diagnosis of the primary tumor. Compared with pancreatic metastases from renal cell cancer, metastases from melanoma and lung cancer were associated with worse survival. The differences in survival of patients with renal cell cancer metastases and those with breast cancer, colorectal, or sarcoma metastases did not reach statistical significance [872].

Gastrointestinal stromal tumor (GIST)

Gastrointestinal stromal tumor represents a subset of gastrointestinal mesenchymal tumors; their clinical manifestations include abdominal uncomfotableness, digestive ulcer, bleeding, and palpable but vague abdominal mass in more than half of the patients. Positive CD117/KIT and CD34 immediately establish the diagnosis of GIST. Expression of KIT is seen in almost all GISTs, regardless of the site of origin, histologic appearance, or biologic behavior, and is therefore regarded as one of the key diagnostic markers. For many years, cases of spindle cell and epithelioid cell neoplasms were taken as smooth muscle tumors, classified previously as leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas, lacking evidence of smooth muscle origin. There are articles reporting such tumors as pancreatic leiomyosarcoma, pancreatic carcinosarcoma, pancreatic schwannoma, and pancreatic epithelioid leiomyoma, among which pancreatic GISTs really should exist. It was reported an extremely rare case of a very large gastrointestinal stromal tumor, GIST, which arose in the pancreatic head with long-time aggressive growth and had characteristic image features as detected in magnetic resonance imaging (MRI) and digital subtraction angiography. A 67-year-old man was found having a mass of 5 cm in diameter in the pancreatic head region 3 years ago by MRI. Pancreatic head carcinoma was diagnosed and stereotactic conformal radiotherapy prescribed. Two months ago, the patient began to have fever, nausea, and vomiting, and MRI revealed a 10 x 9 x 14-cm mass in the pancreatic head, which was lobulated with central necrotic liquefaction and infiltrating the small omentum and the posterior wall of the gastric antrum. Another MRI showed that the large mass increased in size, protruded into the gastrohepatic ligament. Half a month later, the patient died of massive digestive hemorrhage. Postmortem histopathologic result showed GIST of the pancreas invading the neighborhood. Hematoxylin-eosin stain revealed that the tumor tissue consisted mainly of darkly stained spindle cells and occasional epithelioid cells. Immunohistochemistry analysis showed CD117(+), CD34(+), Des(j), S-100(j), and PCK(j) [873].

Complete tumor resection with clear margins including adjacent organs is the treatment of choice for gastrointestinal stromal tumors (GISTs). However, true tumor invasion of adjacent organs has been reported to be rare. Concomitant distal pancreatectomy (DP) for suspected tumor infiltration is not infrequently performed during resection of large gastric GISTs. One study aimed to determine the true frequency of adjacent organ involvement by large gastric GISTs with particular attention to the pancreas and compares the outcome after curative resection with and without a concomitant DP in order to determine if DP is truly necessary. A retrospective review of 37 patients who underwent curative resection of large (≥ 10 cm)

gastric GISTs was conducted. Wedge resections were performed in 22, partial gastrectomies in nine, and total gastrectomies in six patients. The median operative time was 180 min (range, 60-330 min), and the patients had a median postoperative stay of 8 days (range, 4-29 days). Overall, there were eight (22 %) morbidities including two (5 %) mortalities. Nineteen (51 %) had concomitant adjacent organ resection, and these included 15 (41 %) DPs with splenectomies. Direct organ invasion was demonstrated in 5/19 patients (26 %) and 7/30 organs (23 %) resected. Only 1/15 (7 %) DP specimens demonstrated tumor infiltration. Comparison between the patients with and without a concomitant DP demonstrated that performance of a DP was associated with a longer operation time (225 min vs 158 min), increased postoperative stay (9 days vs 8 days), and increased postoperative morbidity (40 % vs 9 %). The DP cohort also had a statistically significant poorer 5-year recurrence free survival (22 % vs 60 %). It was concluded that although adjacent organ involvement is not uncommon with large gastric GISTs, concomitant distal pancreatectomy is usually unnecessary as direct pancreatic invasion is rare. Furthermore, concomitant distal pancreatectomy with splenectomy is associated with an increase in postoperative morbidity [874].

Pancreatic phyllodes tumor

A 37-year-old Japanese man with a solid and cystic pancreatic mass had a CT that revealed a well-demarcated solid and cystic mass measuring approximately 3.0 cm in diameter in the pancreatic body. The patient underwent middle segment pancreatectomy, and the retrieved tumor specimen was found to be a well-demarcated solid and cystic lesion measuring 3.0 x 3.0 cm. On histological examination, the cyst walls were found to be lined with a monolayer of non-atypical tall columnar epithelial cells. The solid areas surrounded the cystic ones and showed storiform proliferation of spindle cells that contained round, oval, or elongated nuclei and were present among abundant collagen fibers. The solid areas sent phylloid projections into the cystic spaces and the main pancreatic duct. The spindle cells were found to be diffusely positive for alpha-smooth muscle actin, desmin, and h-caldesmon on immunohistochemical analysis. Electron microscopy revealed that these cells possessed well-developed myofilaments with dense bodies, pinocytotic vesicles, and basal lumina. Neither metastasis nor local invasion was detected. After the operation (4 years), the tumor has not recurred. The main differential diagnoses of spindle cell tumors are leiomyomas, leiomyosarcomas, inflammatory myofibroblastic tumors, solitary fibrous tumors, extra-gastrointestinal stromal tumors, and schwannomas. However, the histological findings in the present case differed from those of these tumors. The present lesion was the first reported case of a primary pancreatic phyllodes tumor [875].

Castleman disease

Castleman disease (CD) is a rare, benign, and usually systemic lymphoproliferative disorder. Unicentric Castleman disease of the pancreas is extremely rare, with only less than 10 cases described in the literature. It was described a case of an isolated peripancreatic localization of a plasma cell-type Castleman disease, with its clinical presentation, the diagnostic evaluation, and the cure of disease by surgical excision [876].

Lymphoepithelial pancreatic cysts

Pancreatic lymphoepithelial cysts (LECs) are rare pancreatic cystic lesions filled with keratinized material, lined by mature, keratinizing squamous epithelium and surrounded by lymphoid tissue containing few lymphoid follicles. It was reported two cases of surgically

confirmed pancreatic LECs showing a profound restriction of water molecules on diffusion-weighted (DWI) magnetic resonance imaging (MRI). For pancreatic cystic lesions showing lack of molecular motion on DWI with or without thin marginal enhancement on contrast material-enhanced imaging, LECs consisting of internally keratinized materials with restricted diffusion should be considered in differential diagnoses even though they cannot always be easy to distinguish from other focal pancreatic lesions containing mucin, blood clot, or nonliquefactive necrosis [877].

Intrapancreatic spleen

Intrapancreatic accessory spleen (IPAS) can pose a challenge in the diagnostic workup by mimicking a pancreatic neoplasm. Reports of IPAS identified by endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) are scant in the literature, and increased recognition of this benign entity may reduce misdiagnosis and unnecessary surgical intervention. It was reported 2 cases of IPAS diagnosed by EUS-guided FNA biopsy. Each patient underwent computed tomographic evaluation for abdominal pain; it revealed a mass or thickening within the tail of the pancreas. Both patients were referred for EUS-guided FNA to further characterize their pancreatic lesions. In both cases, the cytomorphologic appearance of smears and cell blocks demonstrated aggregates of benign splenic tissue characteristic of both white and red pulp. Rare fragments of pancreatic acinar tissue were also identified. One cell block demonstrated benign splenic and pancreatic parenchyma immediately adjacent to one another without an apparent intervening capsule [878].

Sclerosing mesenteritis

Sclerosing mesenteritis (SM), also known as mesenteric lipodystrophy, rarely involves the parenchyma of the pancreas. When SM does involve the pancreas, it can mimic pancreatic carcinoma both clinically and radiographically with pain, obstructive jaundice, a mass lesion, and even the appearance of vascular invasion. It was reported 6 patients with SM involving the pancreas (mean age 43 years, 5 female), and review their clinical presentation, radiographic findings, pathology, and outcome. Five of these 6 patients were originally thought to have a primary pancreatic neoplasm. Initial presenting clinical information was available for each patient: all 6 reported abdominal or epigastric pain, 3 reported weight loss, and 2 reported one or more of the following: back pain, fever, abdominal bloating/distention, nausea with/without vomiting, and anorexia. The lesions formed masses with an infiltrative pattern and all had 3 key histologic features: fibrosis, chronic inflammation, and fat necrosis-without a known etiology. The inflammatory infiltrate was composed of a mixture of lymphocytes, plasma cells, and scattered eosinophils. Of the 5 patients with post-treatment clinical information available, 4 had at least a partial response to treatment with steroids, tamoxifen, azathioprine, resection, or a combination of these, and 1 did not respond. A dramatic response to immunosuppressive therapy is illustrated by the case of a 46-year-old woman who presented with the presumptive diagnosis of an unresectable pancreatic cancer. Distinguishing SM from pancreatic carcinoma is crucial to appropriate management, as patients with SM may benefit from immunosuppressive therapy [879].

Retroperitoneal fibrosis

It was reported one of few cases of idiopathic retroperitoneal fibrosis of the pancreas, which is different from the classical retroperitoneal fibrosis that affects ureters and vessels that mimicking locally advanced pancreatic carcinoma at presentation [880].

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown etiology affecting patients from all genetic backgrounds. Pancreatic involvement is rare; the first case was described on autopsy in 1937. It was presented a case of pancreatic sarcoidosis without a history of the disease presenting as biliary obstruction mimicking pancreatic malignancy. The patient described presented with all the signs and symptoms of a pancreatic malignancy, which was confirmed on a CT scan; the positron emission tomography scan and the CA 19-9 level were also confirmatory of the suspected diagnosis. In this setting, if the mass looks resectable, a Whipple procedure would be the next logical step. However, such strategy would be aggressive management for a benign condition that could be palliated with diverting rather than resective procedures without changing the outlook of the disease. It was suggested keeping a high index of suspicion in patients with a history of the disease if demographic concordance exists [881].

PANCREATIC ENDOCRINE TUMORS AND ENDOCRINOLOGY

Overview

Neuroendocrine tumours (NETs) are increasing in both incidence and prevalence and, as a group, are more prevalent than either gastric, pancreatic, esophageal or hepatobiliary adenocarcinomas, or any two of these cancers combined. Clinical awareness of the protean and intermittent symptoms of NETs (e.g. sweating, flushing, diarrhoea, and bronchospasm) is critical for timely diagnosis; however, the classical carcinoid syndrome is relatively uncommon. The most useful diagnostic test for gastrointestinal NETs is measurement of plasma chromogranin A (CgA) levels. Disease extent is assessed by both anatomical imaging, and nuclear imaging with radiolabelled somatostatin analogues. Pathological evaluation comprises tumour-node-metastasis classification, a minimum pathological dataset, CgA and synaptophysin immunostaining, as well as mitotic count or Ki-67 index (a marker of cell proliferation) to define grading. Resection of the primary lesion and as much metastatic disease as possible increases the efficacy of medical therapy. Other management strategies include hepatic embolisation and peptide receptor radionuclide therapy. Patients with tumours expressing somatostatin receptors should be treated with somatostatin analogues. Depending on the tumour grade, other effective agents include cytotoxics, tyrosine kinase inhibitors, and antiangiogenics. The overarching requirement for best management of patients with NETs is to ensure that they have ready access to experienced multidisciplinary clinician groups located within centres of appropriate subspecialty expertise [882].

Information on pancreatic endocrine tumors (PETs) comes mostly from small, retrospective, uncontrolled studies conducted on highly selected patients. The aim of one study was to describe the clinical and pathological features of PETs in a prospective, multicenter study. Newly diagnosed, histologically proven, sporadic PETs observed from 2004 to 2007 in 24 Italian centers were included in a specific data set. Two hundred ninety-seven patients (mean age 59 years, females 51 %) were analyzed. In 73 cases (25 %), the tumor was functioning (F) (53 insulinomas, 15 gastrinomas, 5 other syndromes) and in 232 (75 %) it was non-functioning (NF); in 115 cases (39 %), the diagnosis was incidental. The median tumor size was 20 mm (range 2-150). Non-functioning PETs were significantly more represented among carcinomas. Nodal and liver metastases were detected in 84 (28 %) and 85 (29 %) cases, respectively. The presence of liver metastases was significantly higher in the non-functioning PETs than in the functioning PETs (32 % vs 18 %), and in the symptomatic than in the asymptomatic patients (35 % vs 19 %). At the time of recruitment, the majority of patients (251, 85 %) had undergone surgery, with complete resection in 209 cases (83 %). The study points out the high number of new cases of PETs observed, with a high prevalence of non-functioning and incidentally discovered forms. The size of the tumor was smaller and the rate of metastasis was lower than usually reported, suggesting a trend toward an earlier diagnosis [883].

Education

In recent years, there has been a growing interest in endocrine surgery. Educational objectives have been published by the American Association of Endocrine Surgeons (AAES), but data have not been collected describing the recruitment pool, fellowship, or postfellowship experiences. A survey was distributed to endocrine surgeons in practice <7 years and endocrine surgery fellows. Demographic, training, and practice data were collected. The survey response rate was 69 percent (46/67); 85 percent were practicing endocrine surgeons and 15 percent were fellows. In all, 72 percent of respondents

completed an endocrine surgery fellowship, 17 percent completed surgical oncology, and the remaining individuals completed no fellowship. The mean age was 38 (32-49) years; 39 percent were women, 67 percent were white, 26 percent were Asian, 11 percent were Hispanic, and 2 percent were black. A total of 89 percent completed residency at academic centers. Endocrine surgery fellows performed significantly more endocrine surgery cases in residency than the average graduating chief resident. Mentorship was a critical factor in fellows' decisions to pursue endocrine surgery. Fellows graduated with a median (range) of 150 (50-300) thyroid, 80 (35-200) parathyroid, 10 (2-50) neck dissection, 13 (0-60) laparoscopic adrenal, and 3 (0-35) endocrine-pancreas. Fellows felt the least prepared in neck dissection and pancreas. Of the respondents, 76 percent of endocrine surgeons in practice are at academic centers, and 75 percent have practices where most cases are endocrine based. It was concluded that exposure to endocrine surgery and mentorship are powerful factors that influence residents to pursue careers in endocrine surgery. Significant variation is found in the case distribution of fellowships with a relative paucity in neck dissection, pancreas procedures, and research. Recruitment to endocrine surgery should begin in residency, and the standardization of training should be a goal [884].

Epidemiology

Neuroendocrine tumors (NETs) are an unusual family of neoplasms with a wide and complex spectrum of clinical behavior. It was presented the first report of a National Cancer Registry of gastroenteropancreatic neuroendocrine tumors from a Southern European country. Data was provided online at www.retegep.net by participating centers and assessed for internal consistency by external independent reviewers. The study cohort comprised 907 tumors. The most common tumor types were carcinoids (55 %), pancreatic nonfunctional tumors (20 %), metastatic NETs of unknown primary (9%), insulinomas (8 %) and gastrinomas (4 %). Forty-four percent presented with distant disease at diagnosis, most often those from small intestine (65 %), colon (48 %), rectum (40 %) and pancreas (38 %), being most unusual in appendix primaries (1 %). Stage at diagnosis varied significantly according to sex, localization of primary tumor, tumor type and grade. Overall 5-year survival was 75 percent (95 % confidence interval 71 % to 80 %) and was significantly greater in women, younger patients and patients with hormonal syndrome and early stage or lower grade tumors. Prognosis also differed according to tumor type and primary tumor site. However, stage and Ki-67 index were the only independent predictors for survival [885].

Duodenopancreatic neuroendocrine tumors are rare, although current epidemiological studies worldwide suggest an incidence rate increase. It was assessed the pathological incidence of duodenopancreatic neuroendocrine tumors for 18 years in The Netherlands. Standardized excerpts from pathological reports of all patients who had a diagnosis of duodenopancreatic neuroendocrine tumors from 1991 until 2009 were collected from the Pathologisch Anatomisch Landelijk Geautomatiseerd Archief and reviewed. This nationwide network and registry of histopathological and cytopathological data covers 100 percent of the pathological reports in The Netherlands. It was identified 905 patients with pancreatic (n=692) or duodenal (n=213) neuroendocrine tumors. Most of these patients (69 %) had a nonfunctional tumor. Functional tumors were diagnosed at a younger age compared with nonfunctional tumors. The mean annual incidence rates per 1,000,000 persons over 1991 to 2009 were 2.54 for pancreatic and 0.81 for duodenal neuroendocrine tumors. The highest incidence was found in patients 65 to 79 years of age. The incidence of nonfunctional neuroendocrine tumors had increased significantly for two decades [886].

Classification

Neuroendocrine neoplasms (NETs), defined as epithelial neoplasms with predominant neuroendocrine differentiation, arise in most organs of the body and share many common pathologic features. However, a variety of different organ-specific systems have been developed for nomenclature, grading, and staging of NETs, causing much confusion. Although differences persist, there are many common themes, such as the distinction of well-differentiated (low and intermediate-grade) from poorly differentiated (high-grade) NETs and the significance of proliferative rate in prognostic assessment. A recently published minimum pathology data set is presented to help standardize the information in pathology reports. Although an ultimate goal of standardizing the pathologic classification of all NETs, irrespective of primary site, remains elusive, an understanding of the common themes among the different current systems will permit easier translation of information relevant to prognosis and treatment. One semantic issue relates to the use of the term endocrine versus neuroendocrine. Originally, the concept of neuroendocrine neoplasia reflected the hypothesis that the cells from which these tumors were derived originated from the embryonic neural crest. This concept was disproved years ago, causing some authorities to advocate abandoning the term neuroendocrine in favor of endocrine, to reflect that most of these epithelial neoplasms recapitulated cells of endodermal origin. However, the neoplastic cells also possess features of neural and epithelial cells, and for this reason, the most recent edition of the WHO classification of tumors of the digestive system has once again recommended the use of neuroendocrine. The terminology for NETs varies by anatomic site. The use of the term carcinoid tumor has been repeatedly criticized because of concerns that the term does not adequately convey the potential for malignant behavior that accompanies many of these neoplasms. However, carcinoid tumor remains in use, both in the official WHO classification of NETs of the lung and as a synonym for NETs of other sites that retains widespread colloquial usage. The systems of nomenclature reflect differentiation and grading features of NETs. In essentially all systems, a sharp division is made between well-differentiated and poorly differentiated tumors, with the latter group being clearly designated as high-grade neuroendocrine carcinomas (neuroendocrine carcinoma, grade 3), including small-cell carcinoma and large-cell neuroendocrine carcinoma variants. Combined (mixed) forms with elements of non-neuroendocrine carcinoma (usually adenocarcinoma or squamous cell carcinoma) are also well recognized. The distinction of well-differentiated from poorly differentiated NETs is probably one of the most important pathologic assessments related to these neoplasms, as the biologic behavior of the well-differentiated group is often rather indolent, whereas poorly differentiated neuroendocrine carcinomas are very highly aggressive [887].

Molecular biology

PAX (paired box) genes encode a family of transcription factors that regulate organogenesis and cell-lineage specification in multiple organ systems. In the pancreas, PAX proteins play a critical role in islet cell differentiation. It was recently observed that islet cells show strong, diffuse staining for PAX8 by immunohistochemistry. However, PAX8 expression has not previously been examined in pancreatic endocrine tumors (PETs). The purpose of one study was to evaluate PAX8 expression in PETs, and to correlate expression with clinical and pathologic features and behavior. PAX8 expression in other well-differentiated neuroendocrine tumors (WDNETs) was also studied. In total, 190 tumors were evaluated: 156 primary WDNETs (63 PETs, 31 ileal, 5 duodenal, 5 gastric, 19 appendiceal, 13 rectal, and 20 pulmonary carcinoid tumors) and 34 liver metastases (18 PETs and 16 ileal carcinoid tumors). PAX8 was positive in 42/63 (67 %) primary PETs. Expression of PAX8 was significantly associated with WHO category 1.1 ("benign" behavior) compared with category 1.2 (uncertain behavior) or 2 (well-differentiated endocrine carcinoma) (positive in 100 %, 64

%, and 52 % of tumors, respectively). PAX8-positive PETs were also significantly smaller and more often clinically functional; PAX8-negative tumors were more frequently associated with liver metastases. PAX8 expression was not associated with patient age, gender, MIB1 index, or lymph node metastases. PAX8 expression was detected in 0/20 (0 %) pulmonary, 1/5 (20 %) gastric, 5/5 (100 %) duodenal, 0/31 (0 %) ileal, 4/19 (21 %) appendiceal, and 11/13 (85 %) rectal carcinoid tumors. Among the liver metastases, PAX8 was positive in 9/18 (50 %) metastatic PETs compared with 0/16 (0 %) metastatic ileal carcinoid tumors. In summary, PAX8 is expressed in normal pancreatic islet cells and in a high proportion of primary and metastatic PETs. In the GI tract, PAX8 is positive in the majority of duodenal and rectal carcinoid tumors, and in a minor subset of appendiceal and gastric carcinoids. PAX8 expression is absent in ileal and pulmonary carcinoid tumors. PAX8 immunostaining may be helpful in determining the primary site for a WDNET metastatic to the liver, as ileal (PAX8 negative) and pancreatic (PAX8 positive) tumors most often present as a metastasis from an occult primary. PAX8 may also be a prognostic marker in PETs, as loss of expression is associated with malignant behavior [888].

Chromogranin A

Neuroendocrine tumors (NETs) are a form of cancer that differ from other neoplasia in that they synthesize, store, and secrete peptides, e.g., chromogranin A (CgA) and amines. A critical issue is late diagnosis due to failure to identify symptoms or to establish the biochemical diagnosis. A literature review and analysis of the utility of plasma/serum CgA measurements in NETs and other diseases was performed. CgA is a member of the chromogranin family; its transcription and peptide processing are well characterized, but its precise function remains unknown. Levels are detectable in the circulation but vary substantially (approximately 25 %) depending on which assay is used. Serum and plasma measurements are concordant. CgA is elevated in approximately 90 percent of gut NETs and correlates with tumor burden and recurrence. Highest values are noted in ileal NETs and gastrointestinal NETs associated with multiple endocrine neoplasia type 1. Both functioning and nonfunctioning pancreatic NETs have elevated values. CgA is more frequently elevated in well-differentiated tumors compared to poorly differentiated NETs. Effective treatment is often associated with decrease in CgA levels. Proton pump inhibitors falsely increase CgA, but levels normalize with therapy cessation. CgA is currently the best available biomarker for the diagnosis of NETs. It is critical to establish diagnosis and has some utility in predicting disease recurrence, outcome, and efficacy of therapy. Measurement of plasma CgA is mandatory for the effective diagnosis and management of NET disease [889].

Rare symptoms and signs

Splenic involvement in neuroendocrine pancreatic tumors is well known but rarely presents as a primary splenic mass. A rare case of a neuroendocrine tumor involving the tail of the pancreas, splenic hilum and splenic flexure of the colon, forming a conglomerate mass and presenting as isolated gastric varices is described. A 75-year-old male presented with hematemesis and melena. Esophagogastroduodenoscopy revealed isolated gastric varices. A CT scan revealed a mass predominantly involving the spleen and a small part of the pancreas. Thus, a splenic mass with isolated gastric varices should be kept in mind as one of the presentations of a pancreatic neuroendocrine tumor [890].

Effects of sex steroids

The endocrine pancreas is central in the physiopathology of diabetes mellitus. Nutrients and hormones control endocrine pancreatic function and the secretion of insulin and other pancreatic islet hormones. Although the pancreas is not usually considered as a target of steroids, increasing evidence indicates that sex steroid hormones modify pancreatic islet function. The biological effects of steroid hormones are transduced by both, classical and non-classical steroid receptors that in turn produce slow genomic and rapid non-genomic responses. In a review, it was focused on the effects of sex steroid hormones on endocrine pancreatic function, with special emphasis in animal studies [891].

Effects of serotonin

To determine if serotonin production by pancreatic endocrine neoplasms is associated with the pancreatic duct stenosis seen in patients with stenosis that is out of proportion to the size of the tumors seen on computed tomographic images an institutional approval was obtained for a study. Informed consent was waived. Clinical and radiologic findings in six patients were reviewed. Gross and histologic findings in the resected pancreata were also assessed. Formalin-fixed paraffin-embedded tumor sections were immunolabeled with antibodies to serotonin. Tissue microarrays constructed from 47 pancreatic endocrine neoplasms from the institutional tissue bank served as controls. Histologic and serotonin immunoreactivity findings were compared between the two groups. The Fisher exact test was used to compare serotonin immunoreactivity. Only one of the six study patients had a large dominant tumor (4 cm in the pancreatic head). All others were 2.5 cm or smaller. Four of the six pancreatic endocrine neoplasms with associated pancreatic duct stricture had prominent stromal fibrosis. Serotonin immunoreactivity was present in five (83 %) patients, and this labeling was strong and diffuse in the four patients with prominent fibrosis. By contrast, stromal fibrosis was minimal in the nonimmunoreactive case. Only three (6 %) of the 47 control pancreatic endocrine neoplasms were immunoreactive for serotonin. It was concluded that these data suggest that serotonin produced by pancreatic endocrine neoplasms may be associated with local fibrosis and stenosis of the pancreatic duct. Clinicians should be aware that small pancreatic endocrine neoplasms can produce pancreatic duct stenosis resulting in ductal dilatation and/or upstream pancreatic atrophy out of proportion to the size of the tumor [892].

Insulinoma

Preoperative localisation of insulinoma improves cure rate and reduces complications, but may be challenging. To review diagnostic features and localisation accuracy for insulinomas a cross-sectional, retrospective analysis was performed in patients with insulinoma in the years 1990-2009, including sporadic tumors and those in patients with multiple endocrine neoplasia syndromes. Patients were identified from a database, and case notes and investigation results were reviewed. Tumour localisation by computed tomography (CT), magnetic resonance imaging (MRI), octreotide scanning, endoscopic ultrasound (EUS) and calcium stimulation was evaluated. Insulinoma localisation was compared to histologically confirmed location following surgical excision. Thirty-seven instances of biochemically and/or histologically proven insulinoma were identified in 36 patients, of which seven were managed medically. Of the 30 treated surgically, 25 had CT (83 %) and 28 had MRI (90 %), with successful localisation in 16 (64 %) by CT and 21 (75 %) by MRI, respectively. Considered together, such imaging correctly localised 80 percent of lesions. Radiolabelled octreotide scanning was positive in 10 out of 20 cases (50 %); EUS correctly identified 17 lesions in 26 patients (65 %). Twenty-seven patients had calcium stimulation testing, of which 6 (22 %) did not localise, 17 (63 %) were correctly localised, and 4 (15 %) gave discordant or confusing

results. It was concluded that preoperative localisation of insulinomas remains challenging. A pragmatic combination of CT and especially MRI predicts tumour localisation with high accuracy. Radionuclide imaging and EUS were less helpful but may be valuable in selected cases. Calcium stimulation currently remains useful in providing an additional functional perspective [893].

Insulinomas are rare tumors with an estimated incidence of one per 250,000 person-years. Most insulinomas are benign with less than 10 percent demonstrating malignant behavior, the vast majority of which occur in adults. A systemic review of the literature revealed only nine cases of malignant insulinomas occurring in children. Herein, it was presented a case of metastatic malignant insulinoma in a 12-year-old child. The occurrence of this diagnosis in a child, its unusual pattern of metastases and the challenging management of severe hypoglycemia make this case worth reporting [894].

Metastatic insulinomas may present with recurrent life-threatening hypoglycemia. Treatment of hypoglycemia in such patients is difficult and frequently fails to respond to numerous therapeutic agents, requiring continuous dextrose infusion. The authors present the experience with Yttrium-90 radioembolization in a patient with metastatic malignant insulinoma who failed to respond to distal pancreatectomy, systemic chemotherapy with capecitabine and everolimus and medical treatment with somatostatin analogues, diazoxide and corticosteroids. Treatment with repeated Y-90 radioembolization resulted in rapid resolution of hypoglycemic events, allowing discontinuation of dextrose infusion and hospital discharge. However, the effect of Y-90 administration seems to be transient and without evidence of tumor shrinkage in imaging studies [895].

Hyperinsulinism

The authors reported a rare case of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) with congenital neuroblastoma without feature(s) of Beckwith-Wiedemann syndrome. A term newborn with a birth weight of 3,900 g developed hypoglycemia one hour after birth and required up to 20 mg/kg/min of intravenous glucose infusion to maintain euglycemia. Investigations during the critical period revealed an inappropriately high insulin level. An abdominal CT scan revealed a normal pancreas, right suprarenal mass, and liver nodules. A condition of stage 4S neuroblastoma was suspected and supported by an increased ratio of urine vanillylmandelic acid to creatinine. The bone marrow smear was normal. She underwent near total pancreatectomy at the age of 2 months. The suprarenal mass and liver nodules were not found during the operation or during repeated abdominal CT scans at 3 month of age. Spontaneous regression of neuroblastoma was suspected. The pathology of the pancreas was compatible with PHHI [896].

Adult nesidioblastosis

Adult nesidioblastosis is an uncommon cause of hyperinsulinemic hypoglycemia characterized by diffuse islet hyperplasia with beta-cell hypertrophy and atypia. The cause of nesidioblastosis in adults is unclear but may be different from nesidioblastosis in infants. In contrast to infants, a focal form of adult nesidioblastosis (i.e. "nesidioblastoma") has not been documented, although proposed. It was reported a 44-year-old man with symptomatic hypoglycemia and localized nesidioblastosis treated with surgical enucleation resulting in normalization of blood glucose. Postoperative euglycemia has persisted in this patient to date (4 months at the time of manuscript submission) [897].

Zollinger-Ellison syndrome

The secretin stimulation test is the principal diagnostic tool to identify Zollinger-Ellison syndrome (ZES). It was investigated, by intra-individual comparison, which dose of secretin results in the highest diagnostic efficacy to identify the ZES. Fifty-seven paired secretin stimulation tests, using both 0.26 µg/kg and 0.78 µg/kg secretin, performed in 13 ZES patients and 12 controls, were analyzed and the findings confirmed in a validation cohort. A gastrin increase of >100 ng/l was found to be the most sensitive and specific criterion for a positive test. Higher gastrin increases after 0.78 µg/kg compared to 0.26 µg/kg secretin contributed to a slightly more sensitive (83 vs 81 %) but less specific (69 vs 81 %) test. A validation cohort, with 98 tests using 0.26 µg/kg secretin in 21 ZES patients and 39 controls, provided similar results. In ZES patients with normal fasting serum gastrin levels (<100 ng/l), there was no diagnostic benefit from the use of a higher secretin dose. The 0.26 µg/kg secretin stimulation test has the best diagnostic efficacy for the ZES [898].

Gastrinoma has a low incidence, and the pancreas-originated gastrinoma is rare. Pancreatic gastrinoma patients with liver metastases have poor prognosis and short survival. Local treatment to reduce the tumor burden helps to improve symptoms and slows down tumor progression for patients with unresectable tumors. It was reported a case of pancreatic tail gastrinoma with unresectable liver metastases. The patient received a comprehensive minimally invasive interventional treatment, that is, chemoembolization and radiofrequency ablation for liver metastases, and percutaneous transsplenic radiofrequency ablation combined with radioactive ¹²⁵I seed implantation for pancreatic tail gastrinoma. The patient was followed up for more than 20 months, and showed no clear evidence of tumor recurrence. It was then explored the safety and feasibility of percutaneous transsplenic radiofrequency ablation for unresectable pancreatic tail gastrinoma. This transsplenic approach allows minimally invasive therapy and provides a new treatment option not only for patients with unresectable pancreatic tail tumor but also for patients refusing surgery [899].

Somatostatinoma

Somatostatinoma are rare well-differentiated endocrine tumors with malignant behavior arising from the pancreas and duodenum. They are defined by somatostatin positive immunostaining of the majority of tumor cells. The main clinical features are diabetes, diarrhea and biliary lithiasis related to somatostatin production. Somatostatinoma secreting both calcitonin and somatostatin may be unrecognized as a small number of such observations have been published. It was reported a case of a 57-year-old woman referred for weight loss, diarrhea and worsening diabetes. Computer tomography scan revealed multiple hypervascular liver lesions suggestive of metastases. High plasma calcitonin level was evidenced, with normal chromogranin-A value, and high plasma somatostatin results lately communicated. Calcitonin secretion of extra-thyroidal origin was suspected leading to the identification of a pancreatic mass by further multiphase CT. The patient underwent left pancreatectomy with surgical hepatic resection. Histological and immunostaining studies confirmed definitive diagnosis of somatostatinoma secreting both somatostatin and calcitonin. Plasma calcitonin should be measured in the assessment of duodeno-pancreatic endocrine neoplasm. Calcitonin determination is available, more reproducible than other specific pancreatic endocrine markers and could be effective for diagnosis and follow-up of such foregut-derived endocrine neoplasia [900].

Somatostatin influences motility, secretion, and absorption and often has in vivo a modulating, indirect effect on target cells in the gastrointestinal tract. Knowledge on tissue-specific expression of the five somatostatin receptors (SSTRs), their capacities for internalization and downregulation, their subtype-specific intracellular messengers, and the possibility of forming functionally distinct homodimers or heterodimers, has further

complicated the actual in-vivo mechanism of action of somatostatin. SSTR2 knockout mice showed normal circulating gastrin and unchanged acid output, suggesting a high degree of plasticity behind gastric acid secretion. Intestinal inflammation significantly increased somatostatin mRNA in SSTR2 null compared to wild type suggesting that somatostatin mediates inflammation also in SSTR2 null mice. In pancreatic islets of SSTR1-5 null mice no variations of islet size, cellular organization or glucagon or insulin content was shown when compared with null SSTRs and control mice. Although none of the recent findings produced on somatostatin seem ready to be considered for clinical application, recent developments of animal models such as SSTR knockout mice have highlighted promising results to better understand the direct and indirect effects of somatostatin on gastrointestinal tract functions [901].

Somatostatinoma is a very rare neuroendocrine tumor that originates from D cells and accounts for less than 1 percent of all gastrointestinal endocrine tumors. The duodenum is the most frequent site for this tumor, followed by the pancreas. It was described a 46-year-old Chinese woman who developed pancreatic somatostatinoma presenting with the characteristic "inhibitory" syndrome, but the symptoms were obscure and seemingly uncorrelated. This case was also unique for its large tumor size and mixed pathological pattern. Distal pancreatectomy was performed, and the patient has remained well since operation. As the syndromes of somatostatinoma may be obscure and atypical, clinicians should review all clinical findings to obtain an accurate diagnosis. Aggressive surgery is preferred to improve the survival [902].

Multiple endocrine neoplasias (MENs)

It was presented an update on molecular and clinical genetics of solid tumors associated with the various multiple endocrine neoplasias (MEN) syndromes. MEN type 1 (MEN1) describes the association of pituitary, parathyroid, and pancreatic islet cell tumors with a variety of many other lesions. MEN type 2 (MEN2) conditions represent at least four different syndromes that associate pheochromocytoma with medullary thyroid carcinoma, hyperparathyroidism, and a number of other manifestations. Other pheochromocytoma-associated syndromes include von Hippel-Lindau disease; neurofibromatosis 1; the recently defined paraganglioma syndromes type 1, 3, and 4; Carney-Stratakis syndrome; and the Carney triad. Carney-Stratakis syndrome is characterized by the association of paragangliomas and familial gastrointestinal stromal tumors. In the Carney triad, patients can manifest gastrointestinal stromal tumors, lung chondroma, paraganglioma, adrenal adenoma and pheochromocytoma, esophageal leiomyoma, and other conditions. The Carney complex is yet another form of MEN that is characterized by skin tumors and pigmented lesions, myxomas, schwannomas, and various endocrine neoplasias [903].

To identify gene expression alterations associated with insulinoma formation and progression in 2 mouse models of multiple endocrine neoplasia type 1 mice were killed at 12 or 16 months, and pancreatic islets were isolated by enzymatic and physical disruption. Islets were separated by size representing control, normal, hyperplastic, and adenomatous islets. RNA was isolated from these islets and profiled on Sentrix Mouse-6 Expression version 1 BeadChips. Array data were analyzed in GeneSpring. One hundred and one genes that were significantly altered in hyperplastic islets and insulinomas compared with normal islets were identified. Of these, 64 gene elements showed reduced messenger RNA levels and 37 gene elements had increased gene expression compared with control islets. Altered expression of 3 genes, namely, Gata6, Tspan8, and s100a8, was confirmed by quantitative reverse transcription-polymerase chain reaction, and aberrant levels of Tspan8 and Lmo2 protein measured by Western blot correlated with the changes in messenger RNA levels. It was concluded that these results suggest that alterations in gene expression of Gata6, Tspan8,

S100a8, and Lmo2 may act via novel pathways that play functionally important roles in Men1-associated tumor progression [904].

A novel combination of tumors was found in a 68 year-old female with Multiple Endocrine Neoplasia type-1 (MEN 1) that included a cystic pancreatic endocrine neoplasm (CPEN), a pituitary adenoma, and multifocal cholesterol granulomas (MCGs) in the breast, pleura, and the extremities. The pancreatic tumor displayed a single central locule surrounded by a thin rim of neoplastic parenchyma. The tumor showed heterogeneity in the architecture that included glandular, trabecular and solid patterns. The tumor cells of the pancreas were immunohistochemically positive for both endocrine and pancreatic acinar markers including chromogranin A, synaptophysin, glucagon, lipase, and reg protein. Electron microscopy revealed that there were numerous smaller dense-cored neurosecretory granules, larger zymogen-like granules and microvilli on the apical side of the tumor cells. The pancreatic tumor was diagnosed as CPEN with acinar cell features. Analysis of the DNA extracted from the tissues revealed that there is a MEN1 germline mutation in exon 10 codon 527, and somatic mutation in exon 2 codon 32 in the pancreatic tumor, and one base pair deletion in exon 2 codon 79 in the pituitary adenoma [905].

Carcinoids of extrahepatic bile ducts

The objectives of one study were to evaluate the frequency of carcinoid tumors of the extrahepatic biliary ducts (EHBDs) and the pathologic progression and the role of surgery in the management of this disease. It was described two cases of malignant carcinoids of the EHBDs, which presented as common bile duct tumors in two adult male patients, aged 52 and 70 years, who were diagnosed histologically on surgical resection specimens. A comprehensive review of the literature has also been performed with a focus on survival data. Microscopically, the tumors presented herein were composed of relatively small rounded cells with a trabecular or nesting pattern. Both cases were diffusely immunopositive for chromogranin and synaptophysin, and one of them was also focally reactive with somatostatin and pancreatic polypeptide. There was no expression in any of these tumors of thyroid transcription factor-1 (TTF-1), gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP) and prolactin. The tumor showed transmural invasion in both cases, with lymph node metastasis and subcapsular liver tissue infiltration in one. Both patients are alive with no evidence of disease 41 months and 59 months, respectively, after surgery. Despite being extremely uncommon, with only 70 cases reported to date, carcinoids should be included in the differential diagnosis of EHBD tumors. The study emphasizes the necessity of complete surgical resection as the gold standard treatment for these lesions, and the importance of a correct pathologic diagnosis for prognostic implications [906].

Surgery

Pancreatic endocrine tumors (PETs) are usually small, benign or low-grade malignant, and surgery should preserve the pancreatic parenchyma as much as possible. The aim of one study was to evaluate the postoperative and long-term survival of patients undergoing enucleation in small PETs. Of 82 patients having PETs, 46 with tumor less than 4 cm in diameter, without distant metastases and with R0 resection by final pathologic examination, were included in this study. Enucleation was performed when the tumor did not involve the main pancreatic duct and in the absence of peripancreatic lymphadenopathy (group A); a typical resection was carried out in all other cases (group B). The 2 groups were compared regarding postoperative mortality and morbidity, pancreatic fistula, postoperative hospital stay, reoperation, World Health Organization classification, TNM stage, recurrence, and long-term survival. There were 15 patients (33 %) in group A and 31 (67 %) in group B.

Postoperative and long-term results were similar in the 2 groups, whereas World Health Organization classification was significantly different; enucleation was performed more frequently than typical R0 resection in benign tumors. It was concluded that enucleation should be reserved for patients having benign PETs less than 4 cm in diameter and far from the main pancreatic duct [907].

Complications after radical surgery

resection of pancreatic neuroendocrine tumors (PNETs) has a demonstrated survival advantage, further evaluation of the overall morbidity of these procedures is needed. Our objective was to examine a composite outcome of major postoperative complications, including in-hospital mortality. The Nationwide Inpatient Sample (NIS), 1998-2006, was used to identify all patients with a diagnosis of PNET who had undergone pancreatectomy. Candidate predictors consisted of patient and hospital characteristics. A total of 463 (2274 nationally weighted) patients were identified. Overall composite postoperative complication rate was 30 percent. The majority of complications involved infections (11 %), digestive complications (9 %), or pulmonary compromise (7 %). In-hospital mortality rate was 1.7 percent. High Charlson comorbidity score, procedure type of Whipple or total pancreatectomy, and urban hospital location were all associated with significantly increased complication rate. Logistic regression analysis demonstrated: Charlson score of ≥ 3 versus score of 0 (adjusted odds ratio (OR) 4.1, 95 % confidence interval 2.1 to 8.3), surgery type of Whipple or total pancreatectomy versus partial pancreatectomy (adjusted OR 2.7, 95 % confidence interval 1.8 to 4.1), and hospital location of urban versus rural (adjusted OR 4.5, 95 % confidence interval 3.0 to 6.9). It was concluded that while in-hospital mortality rates are low for surgical resection of PNETs, there is a considerable overall postoperative complication rate associated with these procedures. Careful patient and surgery selection may be the key to a surgical treatment approach for PNETs that may optimize outcomes [908].

Capecitabine and temozolomide

Temozolomide is an active agent in metastatic pancreatic endocrine carcinomas. In vitro data indicate that the combination of capecitabine and temozolomide is synergistic for induction of apoptosis in neuroendocrine tumor cell lines. The authors retrospectively evaluated the efficacy of capecitabine and temozolomide in 30 patients with metastatic pancreatic endocrine carcinomas to assess response rate, progression free survival (PFS), and overall survival (OS). Patients with metastatic, well, or moderately differentiated pancreatic endocrine carcinomas who had not received prior systemic chemotherapy were treated with capecitabine (750 mg/m² twice daily, days 1-14) and temozolomide (200 mg/m² once daily, days 10-14) every 28 days. Among 30 patients treated, 21 (70 %) patients achieved an objective radiographic response. Median progression-free survival was 18 months. The rate of survival at two years was 92 percent. Only 4 patients (12 %) experienced grade 3 or 4 adverse events. It was concluded that the combination of capecitabine and temozolomide is associated with an exceptionally high and durable response rate in metastatic endocrine carcinomas of the pancreas. Clinical endpoints, including response rate, survival, and toxicity, are superior to those observed with streptozocin-based regimens [909].

Cisplatin and etoposide

The combination chemotherapy consisting of cisplatin and etoposide, one of the standard regimens for small cell lung cancer, has been widely used to treat extrapulmonary poorly

differentiated neuroendocrine carcinomas. However, there were no prior reports limited to the hepatobiliary tract and pancreas as the primary sites. It was reviewed the cases in a database from 1995 to 2009 and retrospectively examined the clinical data of patients, with unresectable or recurrent poorly differentiated neuroendocrine carcinoma arising from the hepatobiliary tract and pancreas, who received combination chemotherapy with cisplatin and etoposide as the first-line treatment. The chemotherapy regimen consisted of cisplatin 80 mg/m² given intravenously on day 1 and etoposide 100 mg/m² intravenously on days 1-3, repeated every 3-4 weeks. Twenty-one patients were treated with the above regimen of cisplatin and etoposide combination chemotherapy. The primary tumor site was the liver in 2 patients, gallbladder in 8 patients, pancreas in 10 patients and ampulla of Vater in 1 patient. Although no complete responses were obtained, three patients had partial responses, resulting in an overall response rate of 14 percent. Median progression-free survival was 2 months, and median overall survival was 6 months. The major adverse events were myelosuppression and gastrointestinal toxicities, with grade 3 or 4 neutropenia (90 %), nausea (33 %) and anorexia (24 %). It was concluded that cisplatin and etoposide combination as the first-line chemotherapy for hepatobiliary or pancreatic poorly differentiated neuroendocrine carcinoma had only marginal antitumor activity and relatively severe toxicity compared with previous studies on extrapulmonary poorly differentiated neuroendocrine carcinoma treated with the same regimen [910].

Octreotide LAR

Octreotide long acting repeatable (LAR) is commonly used to control the symptoms of patients with functional neuroendocrine tumors. Unfortunately, most patients escape control over time and require higher LAR doses or more frequent rescue therapy to remain asymptomatic. Previous work has shown that body weight and monthly LAR dose will significantly affect circulating plasma octreotide levels in patients undergoing therapy. To determine if other parameters change circulating plasma octreotide levels, it was prospectively studied 82 patients undergoing long-term LAR therapy. Multivariate analysis demonstrated that the plasma octreotide levels decrease by approximately 3.4 percent for each unit of body mass index (BMI) increase, adjusting for sex and monthly LAR dose. Plasma octreotide levels for females were approximately 48 percent higher than those for males, adjusting for BMI and monthly LAR dose. Initial and subsequent octreotide LAR doses should take into consideration sex and BMI. Males are estimated to require 14 mg higher monthly LAR doses than females with the same BMI [911].

PANCREATIC INFECTIOUS DISEASES

Malaria

Falciparum malaria is occasionally associated with multiple organ system complications. However, acute pancreatitis rarely occurs as a part of the spectrum. A 13-year-old boy presented with falciparum malaria complicated predominantly by acute pancreatitis. He recovered satisfactorily with supportive measures. There are less than 10 such documented instances in the literature and they are mostly adults. Acute abdomen in Plasmodium falciparum infection may reveal pancreatitis which should be detected at the earliest [912].

Tuberculosis

Endoscopic ultrasonography guided fine needle aspiration is a useful diagnostic aid in evaluation of cystic pancreatic mass. It was reported a patient with pancreatic tuberculous abscess who presented with pyrexia, and was found to have cystic pancreatic mass on CT scan. Pancreatic tuberculous abscess was diagnosed with the help of endoscopic ultrasound (EUS)-guided fine needle aspiration cytology (FNAC), thereby obviating the necessity for surgery [913].

Actinomycosis

Chronic alcoholic pancreatitis is a debilitating disease that is often complicated by pseudotumoral changes of the pancreas, retroperitoneal fibrosis, and pancreatic cancer. Actinomycosis is an uncommon intra-abdominal infection and its association with chronic pancreatitis has been rarely reported. It was presented a case of a patient with progressive long standing chronic pancreatitis who develops pseudo-tumoural changes and retroperitoneal fibrosis associated with actinomycosis. It was a rare presentation of actinomycosis, posing a diagnostic challenge to the clinician, with important therapeutic implications [914].

Blastomycosis

Paracoccidioidomycosis, or South American blastomycosis, is a systemic mycosis caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is common in Central and South America and was first described by Adolfo Lutz in 1908. Incidence levels are estimated at 1 to 3 cases per 100,000 inhabitants in areas where it is highly endemic, with an annual mortality rate of 1.45/1,000,000 inhabitants. The disease usually appears between the third and sixth decades of life, in two principal forms: the acute or subacute juvenile form, which mainly compromises the reticuloendothelial system, and the chronic form more prevalent in adults, which mainly affects the lungs and the skin. Other organs can also be compromised, including the bones (ribs and clavicles), the brain, the digestive system, urogenital organs, and adrenal glands. Paracoccidioidomycosis is less common in women because of the presence of estrogen, which inhibits the transformation of conidia (inactive form not found by itself) into yeasts (the infectious form), thereby conferring protection from the disease. The agent's principal mode of inoculation is by inhalation, although infection can also occur by cutaneomucous means. The growth of the mycosis in the abdomen can mimic neoplasia when it compromises adjacent structures. Two cases were described in which intra-

abdominal paracoccidioidomycosis behaved like periampullary neoplasia once the exit path from the bile duct had been compromised [915].

PANCREATIC PSEUDOCYSTS AND ANEURYSMS

Pseudocysts

A number of methods are available for the drainage of pancreatic pseudocysts, including percutaneous, endoscopic and open approaches. It was developed a combined radiological and endoscopic technique (predating the use of endoscopic/ultrasound) to allow drainage of pancreatic pseudocysts into the stomach. The aim of the study was to evaluate the long-term results of this approach. It was a retrospective study of patients undergoing combined endoscopic/ultrasound-guided percutaneous stenting between 1994 and 2007. Data were extracted from case records and our computerised radiology database. Thirty-seven combined endoscopic/ultrasound-guided procedures were undertaken. Median patient age was 52 years (range 26-84 years). Nineteen pseudocysts were secondary to acute pancreatitis and 18 were in patients with chronic pancreatitis. The diameter of pseudocysts on pre-procedure imaging ranged from 4 to 21 cm (median 11 cm). Median duration of hospital stay was 7 days (range 1-44 days) and 30-day mortality was 0 percent. Stents were inserted in 70 percent of patients (n=26). Of those patients stented during the combined procedure, three developed infection of the pseudocyst, necessitating open cystgastrostomy within the first month. During a mean follow-up period of 41 months, two patients developed recurrent pseudocysts which were successfully drained with a further combined procedure (16 and 43 months). Repeat imaging in the remainder of patients failed to show any evidence of a persistent or recurrent pseudocyst beyond 2 months. It was concluded that combined radiological and endoscopic drainage is safe, cost-effective and highly efficient in preventing recurrent pseudocyst formation [916].

A 40-year-old man was admitted to our hospital because of epigastralgia and vomiting. His condition was diagnosed as acute pancreatitis with a pancreatic pseudocyst, obstructive jaundice, and duodenal stenosis. Because he had fever, abdominal pain, and elevated levels of C-reactive protein (CRP), endoscopic ultrasound-guided transmural cyst drainage (EUS-CD) was performed with a nasocystic tube on the 6th day. After the cyst was reduced and the patient recovered from the obstructive jaundice and duodenal stenosis, the nasal drainage tube was replaced with a plastic stent. Because a short extent of stenosis in the main pancreatic duct in the pancreatic head was found by endoscopic retrograde cholangiopancreatography (ERCP), a 5Fr pancreatic stent was placed to prevent pancreatitis. No recurrence of pancreatitis and the cyst occurred after removal of both stents 5 days later [917].

Biomarkers

Biomarker detection in pancreatic cyst fluids is of importance to improve the diagnosis of mucinous cystadenoma, a precancerous lesion. However, assay protocols are generally established for serum testing. Immunoradiometric assay of gastric M1/MUC5AC mucin was performed on pancreatic cyst fluids with well-characterized monoclonal antibodies. Among 1466 pancreatic cyst fluids tested, about 10 to 15 percent of samples presented abnormal behaviors: radioactivity measured after immunoradiometric assay much lower than the blank of the assay and increasing dilution of the fluids leading to apparent increase of M1/MUC5AC concentration. In contrast, none of the 109 hepatic cyst fluids tested presented interference. It was demonstrate that some (n=54) interfering fluids cause mucin degradation as well as antibody degradation. Western blot analysis showed that the C-terminal part of the M1/MUC5AC apomucin is most sensitive to degradation. It was concluded that the presence of proteases that degrade antibodies as well as mucin may explain the pitfalls observed in 4 percent of the samples. To detect this interference, each fluid has to be systematically tested at 1:100 dilution in the presence of a saturating concentration of M1/MUC5AC mucin

standard and in the absence of antiprotease reagents. Detection of interference could prevent false results caused by mucin degradation in situ [918].

Percutaneous gastropseudocystostomy

With the emergence of minimally invasive techniques, percutaneous drainage has been applied to the management of symptomatic pancreatic pseudocysts in lieu of conventional surgical or endoscopic therapy. Percutaneous insertion of internalized drainage catheters represents an attractive method for pseudocyst drainage, but has been limited by the usual need for cross-sectional imaging or endoscopic guidance. It was describe the use of a simple fluoroscopically guided technique for percutaneous transgastric cystgastrostomy with internalized drainage catheter placement in two cases [919].

Endoscopic duodenopseudocystostomy

Pancreatic pseudocysts adjacent to the jejunum are typically managed by surgery or percutaneous drainage. Whereas numerous studies have evaluated the role of endoscopic ultrasound (EUS)-guided drainage of pancreatic pseudocysts via the stomach and the duodenum, there are no prior reports on EUS-guided cystojejunostomy. A 45-year-old black male patient with long-standing history of alcohol abuse was admitted to our institution with severe abdominal pain, nausea, and vomiting of 72 hours' duration. Physical examination was significant for epigastric tenderness. Laboratory investigations revealed a white blood cell count of $21.6 \times 10^3/\mu\text{L}$ and a serum albumin of 1 mg/dL. A computed tomogram of the abdomen revealed peripancreatic inflammation and a large pancreatic pseudocyst measuring 18×12 cm compressing the proximal jejunum and causing intestinal obstruction. As the location of the pseudocyst made it not amenable for surgical cystogastrostomy and because of the high risk for fistula formation with percutaneous drainage techniques, an EUS-guided drainage was attempted. In addition, his poor nutritional status made him a high-risk candidate for surgical cystojejunostomy that involves mobilization of a Roux-en-Y limb. After decompressing the stomach using nasogastric suction, an EUS examination was undertaken using a therapeutic echoendoscope. The proximal jejunum was intubated under fluoroscopic guidance by continuous aspiration of air, manual compression of the abdomen, and utilizing clockwise torque and withdrawal movements of the echoendoscope to avoid looping. Although the lumen of the proximal jejunum was compressed, it was difficult to appreciate an area of focal prominence. Under EUS guidance, the pseudocyst was identified and accessed using a 19-gauge needle. Care was taken to ensure that the tip of the echoendoscope was straight and not deflected so as to facilitate easy puncture of the pseudocyst with the fine-needle aspiration biopsy needle. After coiling a 0.035-in guidewire within the pseudocyst and dilating the transmural tract to 6 mm, a 7F 4-cm double-pigtail plastic stent was deployed. Approximately 500 mL of clear cyst contents were aspirated after transmural stenting. After the procedure, the patient reported being asymptomatic at 24 hours and was able to tolerate oral intake. A follow-up computed tomogram of the abdomen at 1 week revealed near-complete resolution of the pseudocyst and resolved intestinal obstruction. At 6-month follow-up, the patient was doing well without any symptom recurrence, and the transjejunal stent was retrieved by enteroscopy [920].

NOTES treatment

It was presented a case report of a novel hybrid natural orifice transluminal endoscopic surgery (NOTES). The operation performed was a transgastric cystgastrostomy with endoscopic guidance for a pancreatic pseudocyst. This operation was completed entirely through an existing gastrostomy site with no incisions, thus avoiding the peritoneal cavity. This was a case of a 7-year-old boy with neurologic impairment from congenital herpes simplex virus encephalitis who is tube fed. He had acute pancreatitis and developed a 9 cm

pancreatic pseudocyst. The pseudocyst failed to resolve after 6 weeks and developed a mature wall. Due to a history of multiple abdominal surgeries and known abdominal adhesions, a minimally invasive approach that would avoid entering the peritoneal cavity was the desired approach. The technique involved a trans-oral endoscope for visualization and the use of the gastrostomy as access to the gastric lumen and pseudocyst. The pancreatic pseudocyst was stabilized with two T-fasteners and confirmed with needle aspiration under endoscopic visualization. The pseudocyst was then opened with the LigaSure (Valleylab, Boulder, CO). The cystgastrostomy anastomosis was completed with an Endopath ETS-Flex Articulating Linear Stapler/Cutter (Ethicon Endo-Surgery, Inc, Cincinnati, OH). The operation took less than 2 hours and was completed without an incision. The patient did well postoperatively and had a dramatic reduction in size of the pancreatic pseudocyst to 3.5 cm by 2 weeks [921].

Proteases in cyst fluids

Biomarker detection in pancreatic cyst fluids is of importance to improve the diagnosis of mucinous cystadenoma, a precancerous lesion. However, assay protocols are generally established for serum testing. Immunoradiometric assay of gastric M1/MUC5AC mucin was performed on pancreatic cyst fluids with well-characterized monoclonal antibodies. Among 1466 pancreatic cyst fluids tested, about 10 to 15 percent of samples presented abnormal behaviors: (i) radioactivity measured after immunoradiometric assay much lower than the blank of the assay and (ii) increasing dilution of the fluids leading to apparent increase of M1/MUC5AC concentration. In contrast, none of the 109 hepatic cyst fluids tested presented interference. It was thus demonstrated that some (n=54) interfering fluids cause mucin degradation as well as antibody degradation. Western blot analysis showed that the C-terminal part of the M1/MUC5AC apomucin is most sensitive to degradation. It was concluded that the presence of proteases that degrade antibodies as well as mucin may explain the pitfalls observed in 4 percent of the samples. To detect this interference, each fluid has to be systematically tested at 1:100 dilution in the presence of a saturating concentration of M1/MUC5AC mucin standard and in the absence of antiprotease reagents. Detection of interference could prevent false results caused by mucin degradation in situ [922].

With fungal infection

It was reported the attainment of micafungin concentrations from brain tissue and pancreatic pseudocyst fluid from two patients with invasive candidiasis. Micafungin was present in low levels at both body sites, indicating limited penetration into central nervous system (CNS) tissue and pancreatic fluid. Further studies are needed to fully characterize its pharmacokinetics at these locations, as micafungin may potentially serve as an alternative antifungal therapy for CNS or pancreatic candidal infections for which the currently recommended first-line therapy fails [923].

In Crohn's disease

Pancreatitis has been described occasionally in association with Crohn's disease in adults before, but it is uncommon in children. It may be caused by multiple etiologies, and there exist a few reports of pancreatitis in pediatric patients with inflammatory bowel disease because of biliary obstruction or drug induced. It was reported a rare case of a 14-year-old girl with Crohn's disease and hypoparathyroidism who suffered from hemorrhagic necrotizing pancreatitis with development of huge pseudocysts, a life-threatening complication that required surgical treatment [924].

Intrahepatic

Intrahepatic pancreatic pseudocyst extension is a rare but complex clinical entity requiring multimodality approach for management. There is no consensus regarding the optimal strategy for the treatment of intrahepatic pancreatic pseudocyst and the literature is limited to a few case reports. Most of the published cases were managed by surgical or percutaneous drainage. It was now reported a case of intrahepatic pancreatic pseudocyst extension which failed to resolve by percutaneous drainage. Endoscopic transpapillary drainage was utilized which led to complete resolution of the intrahepatic pancreatic pseudocyst [925].

Aneurysms

It was presented a case of a male patient diagnosed with a large inferior pancreaticoduodenal artery (IPDA) aneurysm, associated with a fresh thrombotic occlusion of the celiac trunk. Given the risk of splanchnic ischaemia, radiologic embolisation of the aneurysm combined with celiac axis stenting was deemed unsafe. Management was therefore modified to elective revascularisation of the celiac axis prior to surgical resection of the aneurysm. A retropancreatic aorto-gastroduodenal artery bypass graft was performed prior to exposing and resecting the pancreaticoduodenal artery aneurysm. This ensured near uninterrupted retrograde supply to the celiac axis during the procedure. This is an effective, efficient and expeditious patient pathway for these rare and complex aneurysms complicated by celiac trunk involvement [926].

Most inferior pancreaticoduodenal artery (IPDA) aneurysms are ruptured at presentation causing a high mortality risk. Minimally invasive treatment approaches may improve overall outcomes in such patients. Between 1996 and 2007, seven patients (5 Males; mean age 55 years) with symptomatic IPDA aneurysms and severe degree (>75 %) celiac artery stenosis were treated with percutaneous transcatheter arterial embolization (TAE). The medical and imaging records were reviewed for demographics, clinical presentation, treatment, complications and follow-up. Patients presented with epigastric pain (7/7), hemodynamic shock (2/7) and rectal bleeding (2/7). Selective catheter angiography was performed in all patients with the intent to embolize the aneurysms. A total of nine aneurysms were seen in seven patients. Two patients had two aneurysms each. The aneurysms ranged in size from 0.5 to 4.0 cm (mean 1.9 cm). Trans-catheter coil embolization was successful in 8/9 aneurysms in 6 patients. Following unsuccessful TAE of one aneurysm in one of the patient, the aneurysm was treated successfully with direct CT-guided percutaneous transabdominal injection of N-butyl-2-cyanoacrylate. There were no complications on follow up. Angioplasty and stenting of the celiac artery were performed in one patient for complete occlusion. None of the patients developed clinical or imaging evidence of visceral ischemia following embolization. None had recurrent symptoms during clinical follow-up (median 3 years, range 0.5-13.5 years). Follow-up CT (median 7 months, range 4 days-12 years) in all patients showed no recurrence of the aneurysm. It was concluded that IPDA aneurysms associated with celiac axis stenosis can be successfully treated with percutaneous embolization with minimal recurrence [927]

NUTRITION IN PANCREATIC DISEASE

A survey of nutrient and food oral intake was undertaken to clarify problems in nourishment support of chemotherapy outpatients with cancer diseases. The ingestion frequency survey (Food Frequency Questionnaire Based on Food Groups: FFQg) of nutrient and food intake was carried out in 54 patients, after chemotherapy at an outpatient clinic in Japan during three weeks 2007. Among them, 50 patients (93 %) reported a valid response (14 breast, 13 colon, 6 stomach, 9 pancreas, and 8 other cancers). Body mass index (BMI; mean \pm SD) was 18.0 ± 1.2 in pancreas cancer patients. BMIs in stomach or pancreas cancer patients were significantly low compared to those in patients with breast, colon, or other cancers. Each group's caloric intake per standard weight (kcal: mean \pm SD) was 29.1 ± 5.0 in pancreas. No significant differences were recognized among the different cancer types. In conclusion, oral intake in chemotherapy outpatients was secured from the result for each type of cancer; however, BMI was low in outpatients with stomach or pancreas cancer in spite of ingestion of food enough to maintain standard weight [928].

PANCREATIC TRAUMA

Traumatic pancreatic rupture is associated with high morbidity and mortality. The diagnosis is difficult and usually accompanied with other injuries. It was reported a 17-year-old adolescent boy who experienced this disease alone. The diagnosis was first suspected in ultrasonography and then confirmed by computed tomography. Endoscopic retrograde pancreatography showed his pancreatic duct was patent. He made an uneventful recovery after 10 days of hospitalization. Ultrasonography is well known for detecting the presence of hemoperitoneum in blunt abdominal trauma. Furthermore, it can be applied to the assessment of patients with posttraumatic abdominal pain. It provides a real-time, noninvasive, and inexpensive means for screening this kind of patients [929].

Imaging

Blunt pancreatic trauma is an exceedingly rare but life-threatening injury with significant mortality. Computed tomography (CT) is commonly employed as the initial imaging modality in blunt trauma patients and affords a timely diagnosis of pancreatic trauma. The CT findings of pancreatic trauma can be broadly categorized as direct signs, such as a pancreatic laceration, which tend to be specific but lack sensitivity and indirect signs, such as peripancreatic fluid, which tend to be sensitive but lack specificity. In patients with equivocal CT findings or ongoing clinical suspicion of pancreatic trauma, magnetic resonance cholangiopancreatography (MRCP) may be employed for further evaluation. The integrity of the main pancreatic duct is of crucial importance, and though injury of the duct may be strongly suggested upon initial CT, MRCP provides clear delineation of the duct and any potential injuries. One article aimed to review and illustrate the CT and magnetic resonance imaging findings of blunt pancreatic trauma and delineate the integration of these modalities into the appropriate imaging triage of severely injured blunt trauma patients [930].

Rest after earlier trauma as a weak point

A girl aged 21 months and a boy aged 3 years both died of hemorrhage from intestinal and mesenteric lacerations due to inflicted blunt abdominal trauma. Histologic examination of sections from the areas of duodenal and mesenteric lacerations confirmed changes of acute injury with hemorrhage, acute inflammatory infiltrates, and surface fibrin deposition. In addition, in both cases, there was also evidence of much longer-standing trauma with mesenteric fibrosis and hemosiderin-containing macrophages (the latter in keeping with previous hemorrhage). In the absence of a history of surgery and local inflammatory disease, these findings suggest that these children had suffered previous abdominal trauma, possibly from similar types of injuries. Scarring of the mesentery and intestine in cases of lethal childhood blunt abdominal trauma may provide evidence of previous similar, significant although sublethal tissue damage. Extensive histologic sampling of abdominal organs and tissues including the mesentery can, therefore, be extremely useful in such cases [931].

PANCREATIC TRANSPLANTATION OVERVIEWS

Review

As result of improved surgical techniques and newer immunosuppressive regimens contributing significantly to better graft survival, exocrine pancreas transplantation remains the standard treatment of choice for patients with diabetes mellitus complicated by end-stage renal disease. Histologic assessment continues to play an important role in the diagnosis of graft complications after pancreas transplantation, especially for evaluating allograft rejection where histopathology is still considered the gold standard. A review elaborates on the current types of pancreas transplants and focuses on the patterns of allograft injury that are encountered in posttransplantation pancreas biopsies along with the pertinent differential diagnoses. In addition to optimal histologic assessment, as in any other organ transplant setting, clinical information including indication and duration of transplant as well as other serologic work-up must be taken into consideration during clinical decision making for optimal graft outcome [932].

In diabetes type 2

The use of pancreas transplantation for type 2 diabetes mellitus is an emerging concept. Several lines of laboratory and clinical evidence suggest that in a carefully selected group of patients, long-term glycemic control and allograft function are similar to that observed for pancreas transplants performed for type 1 diabetes [933].

Pancreas after living donor kidney transplant

One of the alternative options to simultaneous pancreas-kidney transplantation (SPKT) for type I diabetics with renal failure is sequential transplant of a living donor kidney followed by a deceased donor pancreas transplant (pancreas after living donor kidney transplant, PALK). We retrospectively compared the outcomes of SPKT versus PALK. Adults (age 18-59 years) with type I diabetes who were waitlisted for kidney-pancreas and received a SPKT or PALK between 2000 and 2007 were now studied. It was compared patient, kidney graft, and pancreas graft survival. Of 11,966 patients who received a kidney transplant, 807 received a PALK and 5580 received a SPKT. Median time to pancreas from kidney transplant was 336 (25-75 %: 185-602 days) days. Average hospital stay for SPKT recipients was 13 ± 15 days, whereas for PALK recipients was 6 ± 4 days and 10 ± 8 days for kidney and pancreas transplants, respectively. After controlling for confounding factors, patients receiving PALK had better patient survival (HR 0.52; 95 % confidence interval 0.39 to 0.70) and kidney survival (HR 0.48; 95 % confidence interval 0.39 to 0.60) but worse pancreas survival (HR 1.37; 95 % confidence interval 1.16 to 1.62) compared with SPKT. Thus, among those who were waitlisted for a kidney-pancreas transplant, 53 percent received a kidney-pancreas transplant. Of those who received a kidney-pancreas transplant, 87 percent patients underwent SPKT and 13 percent underwent PALK. PALK was associated with better kidney graft and patient survival compared with SPKT. It was found an inferior pancreas graft survival and longer total transplant hospitalization in PALK [934].

Infections after transplantation

Pancreas transplantation (PT) provides the best glycemic control option for diabetes mellitus but is associated with significant morbidities related to infectious disease. It was performed a retrospective study of a cohort of consecutive PT recipients in whom PT was performed from 1998 to 2006 (n=216) and followed up them until 2008. Data regarding infections, rejection, infection chemoprophylaxis, graft failure, absolute lymphocyte counts (ALCs), and mortalities were collected. Simultaneous pancreas and kidney, pancreas transplantation alone, and pancreas after kidney (PAK) transplantations were performed in 42, 67, and 107 patients, with a mean age at transplantation of 47, 41, and 44 years. Of the simultaneous pancreas and kidney, pancreas transplantation alone, and PAK transplant recipients, 55 percent, 37 percent, and 59 percent were men. Overall, 63 percent developed a serious infection during the median follow-up of 6.4 years. Mean (range) number of infectious episodes was 2.3 (1-12), with mostly bacterial infections both within (68 %) and after 1 year (78 %). Incidence of bacterial and viral infections was greatest in the first 3 months after transplantation. Fungal infections were more constant. Bladder exocrine drainage was significantly associated with higher risk of infection (hazard ratio 2.5). Infection within the first 3 months after transplantation was related to higher mortality after the first 3 months (hazard ratio 3.19). Absolute lymphocyte counts was significantly associated with the risk of first infections and bacterial infections. It was concluded that the incidence of infections after pancreatic transplantation was 63 percent and mostly bacterial. Bladder drainage increases infection risk and low absolute lymphocyte counts partially predicts episodes [935].

REFERENCES

001. Beger HG, Gansauge F. Master of surgery in Archiv für Klinische Chirurgie. Langenbecks Arch Surg 2010; 395 suppl 1: 17-21.
002. Bradley EL, Dexter ND. Management of severe acute pancreatitis: a surgical odyssey. Ann Surg 2010; 25: 6-17.
003. Leach SD, Gorelich FS, Modlin IM. Acute pancreatitis at its centenary. The contribution of Reginald Fitz. Ann Surg 1990; 212: 109-10.
004. Schnelldorfer T, Adams DB, Warsaw AL, Lillemoe KD, Sarr MG. Forgotten pioneers of pancreatic surgery: Beyond the favorite few. Ann Surg 2008; 247: 191-202.
005. Pannala R, Kidd M, Modlin IM: Acute pancreatitis. A historical perspective. Pancreas 2009; 38: 355-66.
006. Nordmann O. Neuere Anschauungen über die akute Pankreasnekrose und ihre Behandlung. Arch Klin Chir 1938; 193: 370-82 (in German).
007. Halsted WS. Retrojection of bile into the pancreas, a cause of acute hemorrhagic pancreatitis. Johns Hopkins Hosp Bull 1901; 12: 179-82.
008. Senn N. The Surgery of the Pancreas. Philadelphia, Dorman, 1886, pp 71-107.
009. Rocha FG, Balakrishnan A, Ashley SW, Clancy TE. A historic perspective on the contributions of surgeons to the understanding of acute pancreatitis. Am J Surg 2008; 196: 442-9.
010. Schmieden V, Sebening W. Chirurgie des Pankreas. Arch Klin Chir 1927; 148: 319-87 (in German).
011. Siler VE, Wulsin JH. Consideration of the lethal factors in acute pancreatitis. Arch Surg 1951; 63: 496-504.
012. Walzel P. Zur Diagnose und Therapie der akuten Pankreasnekrose. Bruns' Beitr 1929; 147: 3-13.
013. Morton J. Acute pancreatitis. Surgery 1945; 17: 475-91.
014. Demel R: Umstrittene Fragen bei akuter Pankreasnekrose (Aktuelles zur Aetiologie, Diagnose und Behandlung der akuten Pankreasnekrose). Wien Klin Wochenschr 1936; 49: 1273-8; 1309-12.
015. Paxton JR, Payne JH. Acute pancreatitis. A statistical review of 307 established cases of acute pancreatitis. Surg Gynecol Obstet 1948; 86: 69-75.
016. Watts GT. Total pancreatectomy for fulminant pancreatitis. Lancet 1963; 13: 384.
017. Edelman G, Boutelier P. Le traitement des pancréatites aiguës nécrosantes par l'ablation chirurgicale précoce des portions nécrosées. Chirurgie (Paris) 1974; 100: 155-67.
018. Leger L, Chiche B, Ghouti A Notre expérience de la pancréatite aiguë. Chirurgie (Paris) 1977; 103: 846-7.
019. Mercadier M: Sur une série de 100 cas de pancréatite aiguë graves opérés précocement. Chirurgie (Paris) 1977; 103: 835-45.
020. Alexandre JH, Chambon H, Assan R. Total pancreatectomy in the treatment of acute necrotising and hemorrhagic pancreatitis. Indications – technique. Langenbecks Arch Chir 1976 1976; 340: 231-47.

021. Kümmerle F, Neher M, Schönborn H, Mangold G. Vorzeitige Operation bei akuter hämorrhagisch-nekrotisierender Pankreatitis. *Dtsch Med Wochenschr* 1975; 100: 2241-5.
022. Neher M, Kümmerle F, Mangold G, Schönborn H. Verzögerte Operation bei akuter Pankreatitis. *Chirurg* 1977; 48: 439-43.
023. Beger HG. Management of pancreatic necrosis and pancreatic abscess. In: Carter DC, Warshaw AL (eds): *Pancreatitis*. Edinburgh, Churchill Livingstone, 1989, vol 16, pp 107-19.
024. Elliott DW, Zollinger RM, Moore R, Ellison EH. The use of human serum albumin in the management of acute pancreatitis. Experimental and clinical observations. *Gastroenterology* 1955; 28: 563-87.
025. Elliott DW. Treatment of acute pancreatitis with albumin and whole blood. *Arch Surg* 1957; 75: 573-80.
026. Lankisch PG, Koop H, Winckler K, Quellhorst E, Schmidt H. Experimental model for peritoneal dialysis in small laboratory animals. *Clin Nephrol* 1975; 4: 251-2.
027. Lankisch PG, Koop H, Winckler K, Schmidt H. Continuous peritoneal dialysis as treatment of acute experimental pancreatitis in the rat. I. Effect on length and rate of survival. *Dig Dis Sci* 1979; 24: 111-6.
028. Amundsen E, Ofstad E, Hagen PO. Experimental acute pancreatitis in dogs. I. Hypotensive effect induced by pancreatic exudate. *Scand J Gastroenterol* 1968; 3: 659-64.
029. Satake K, Rozmanith JS, Appert HE, Carballo J, Howard JM. Hypotension and release of kinin-forming enzyme into ascitic fluid exudate during experimental pancreatitis in dogs. *Ann Surg* 1973; 177: 497-502.
030. Hagen PO, Ofstad E, Amundsen E. Experimental acute pancreatitis in dogs. IV. The relationship between phospholipase A and the histamine-releasing hypotensive effects of pancreatic exudate. *Scand J Gastroenterol* 1969; 4: 89-96.
031. Ofstad E, Amundsen E, Hagen PO. Experimental acute pancreatitis in dogs. II. Histamine release induced by pancreatic exudate. *Scand J Gastroenterol* 1969; 4: 75-9.
032. Lankisch PG, Koop H, Winckler K, Schmidt H. Continuous peritoneal dialysis as treatment of acute experimental pancreatitis in the rat. II. Analysis of its beneficial effect. *Dig Dis Sci* 1979; 24: 117-22.
033. Stone HH, Fabian TC. Peritoneal dialysis in the treatment of acute alcoholic pancreatitis. *Surg Gynecol Obstet* 1980; 150: 878-82.
034. Cooper MJ, Williamson RCN, Pollock AV. The role of peritoneal lavage in the prediction and treatment of severe acute pancreatitis. *Ann Roy Coll Surg Engl* 1982; 64: 422-5.
035. Kivilaakso E, Lempinen M, Mäkeläinen A, Nikki P, Schröder T. Pancreatic resection versus peritoneal lavation for acute fulminant pancreatitis. *Ann Surg* 1984; 199: 426-31.
036. Mayer AD, McMahon MJ, Corfield AP, Cooper MJ, Williamson RCN, Dickson AP, Shearer MG, Imrie CW. Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. *N Engl J Med* 1985; 312: 399-404.
037. Ihse I, Evander A, Holmberg JT, Gustafson I. Influence of peritoneal lavage on objective prognostic signs in acute pancreatitis. *Ann Surg* 1986; 204: 122-7.
038. Teerenhovi O, Nordback I, Eskola J. High volume lesser sac lavage in acute necrotizing pancreatitis. *Br J Surg* 1989; 76: 370-3.

039. Ranson JHC, Berman RS. Long peritoneal lavage decreases pancreatic sepsis in acute pancreatitis. *Ann Surg* 1990; 211: 708-18.
040. Schröder T, Sainio V, Kivisaari L, Puolakkainen P, Kivilaakso E, Lempinen M. Pancreatic resection versus peritoneal lavage in acute necrotizing pancreatitis. A prospective randomized trial. *Ann Surg* 1991; 214: 663-6.
041. Platell C, Cooper D, Hall JC. Acute pancreatitis: effect of somatostatin analogs and peritoneal lavage. A meta-analysis of peritoneal lavage for acute pancreatitis. *J Gastroenterol Hepatol* 2001; 16: 689-93.
042. Balldin G, Borgström A, Genell S, Ohlsson K: The effect of peritoneal lavage and aprotinin in the treatment of severe acute pancreatitis. *Res Exp Med* 1983; 183: 203-13.
043. Berling R, Borgström A, Ohlsson K. Peritoneal lavage with aprotinin in patients with severe acute pancreatitis. Effects on plasma and peritoneal levels of trypsin and leukocyte proteases and their major inhibitors. *Int J Pancreatol* 1998; 24: 9-17.
044. Arnold F, Doyle PJ, Bell G. Acute pancreatitis in a patient treated with cimetidine. *Lancet* 1978; i:382-3.
045. Hadas N, Wapnick S, Grosberg SJ, Sugaar S. Cimetidine induced mortality in experimental pancreatitis. *Gastroenterology* 1979; 76: 1148 (abstract).
046. Evander A, Ihse I. Cimetidine treatment in acute experimental pancreatitis. *Eur Surg Res* 1980; 12: 301-9.
047. Lankisch PG, Koop H, Winckler K, Otto J. Cimetidine: harmful in acute experimental pancreatitis? *Hepatogastroenterology* 1982; 29: 195-7.
048. Morimoto T, Noguchi Y, Sakai T, Shimbo T, Fukui T. Acute pancreatitis and the role of histamine-2 receptor antagonists: a meta-analysis of randomized controlled trials of cimetidine. *Eur J Gastroenterol Hepatol* 2002; 14: 679-86.
049. Meshkinpour H, Molinari MD, Gardner L, Berk JE, Koehler FK. Cimetidine in the treatment of acute alcoholic pancreatitis. *Gastroenterology* 1979; 77: 687-90.
050. Sillero C, Perez-Mateo M, Vazquez N, Martin A.: Controlled trial of cimetidine in acute pancreatitis. *Eur J Clin Pharmacol* 1981; 21: 17-21.
051. Broe PJ, Zinner MJ, Cameron JL. A clinical trial of cimetidine in acute pancreatitis. *Surg Gynecol Obstet* 1982; 154: 13-6.
052. Lojudice TA, Lang J, Metha H, Santa L. Treatment of acute alcoholic pancreatitis: the roles of cimetidine and nasogastric suction. *Am J Gastroenterol* 1984; 79: 553-8.
053. Navarro S, Ros E, Aused R, García-Pugés AM, Piqué JM, Vilar Bonet J. Comparison of fasting, nasogastric suction and cimetidine in the treatment of acute pancreatitis. *Digestion* 1984; 30: 224-30.
054. Cameron JL, Mehigan D, Zuidema GD. Evaluation of atropine in acute pancreatitis. *Surg Gynecol Obstet* 1979; 148: 206-8.
055. Knight MJ, Condon JR, Smith R. Possible use of glucagon in the treatment of pancreatitis. *BMJ* 1971; ii: 440-2.
056. Waterworth MW, Barbezat GO, Hickman R, Terblanche J. A controlled trial of glucagon in experimental pancreatitis. *Br J Surg* 1976; 63: 617-20.
057. Condon RE, Woods JH, Poulin TL, Wagner WG, Pissiotis CA. Experimental pancreatitis treated with glucagon or lactated Ringer solution. *Arch Surg* 1974; 109: 154-8.

058. Lankisch PG, Winckler K, Bokermann M, Schmidt H, Creutzfeldt W. The influence of glucagon on acute experimental pancreatitis in the rat. *Scand J Gastroenterol* 1974; 9: 725-9.
059. Papp M, Ribet A, Fodor I, Németh PÉ, Fehér S, Horváth JE, Folly G. Glucagon treatment of experimental acute pancreatitis. *Acta Med Acad Sci Hung* 1975; 32: 105-16.
060. Dürr HK, Weihe W, Bode C, Bode JC. A controlled trial of glucagon in acute experimental pancreatitis in rats. *Z Gastroenterol* 1977; 15: 728-33.
061. Manabe T, Steer ML. Experimental acute pancreatitis in mice. Protective effects of glucagon. *Gastroenterology* 1979; 76: 529-34.
062. Medical Research Council Multicentre Trial of Glucagon and Aprotinin: Death from acute pancreatitis. *Lancet* 1977; ii: 632-5.
063. Dürr HK, Maroske D, Zelder O, Bode JC. Glucagon therapy in acute pancreatitis. Report of a double-blind trial. *Gut* 1978; 19: 175-9.
064. Gauthier A, Gillet M, Di Costanzo J, Camelot G, Maurin P, Sarles H. Étude contrôlée multicentrique de l'aprotinine et du glucagon dans le traitement des pancréatites aiguës. *Gastroenterol Clin Biol* 1978; 2: 777-84.
065. Olazabal A, Fuller R. Failure of glucagon in the treatment of alcoholic pancreatitis. *Gastroenterology* 1978; 74: 489-91.
066. Debas HT, Hancock RJ, Soon-Shiong P, Smythe HA, Cassim MM. Glucagon therapy in acute pancreatitis: prospective randomized double-blind study. *Can J Surg* 1980; 23: 578-80.
067. Kronborg O, Bülow S, Joergensen PM, Svendsen LB. A randomized double-blind trial of glucagon in treatment of first attack of severe acute pancreatitis without associated biliary disease. *Am J Gastroenterol* 1980; 73: 423-5.
068. Medical Research Council Multicentre Trial: Morbidity of acute pancreatitis: the effect of aprotinin and glucagon. *Gut* 1980; 21: 334-9.
069. Schmidt H, Hesch R-D, Hüfner M, Paschen K, Creutzfeldt W. Hemmung der exokrinen Pankreassekretion des Menschen durch Calcitonin. *Dtsch Med Wochenschr* 1971; 96: 1173-5 (in German).
070. Goebell H, Ammann R, Herfarth C, Horn J, Hotz J, Knoblauch M, Schmid M, Jaeger M, Akovbiantz A, Linder E, Abt K, Nüesch E, Barth E (The Pancreatitis Study Group): A double-blind trial of synthetic salmon calcitonin in the treatment of acute pancreatitis. *Scand J Gastroenterol* 1979; 14: 881-9.
071. Paul F, Ohnhaus EE, Hesch RD, Chemnitz G, Hoppe-Seyler R, Henrichs HR, Hartung H, Waldmann D, Kunze K, Barth E, Nüesch E, Abt K. Einfluß von Salm-Calcitonin auf den Verlauf der akuten Pankreatitis. Ergebnisse einer prospektiven Doppelblindstudie. *Dtsch Med Wochenschr* 1979; 104: 615-22 (in German).
072. Martinez E, Navarrete F. A controlled trial of synthetic salmon calcitonin in the treatment of severe acute pancreatitis. *World J Surg* 1984; 8: 354-9.
073. Smith M, Kocher HM, Hunt BJ. Aprotinin in severe acute pancreatitis. *Int J Clin Pract* 2010; 64: 84-92.
074. Trapnell JE, Rigby CC, Talbot CH, Duncan EHL. A controlled trial of Trasylol in the treatment of acute pancreatitis. *Br J Surg* 1974; 61: 177-82.

075. Imrie CW, Benjamin IS, Ferguson JC, McKay AJ, Mackenzie I, O'Neill J, Blumgart LH. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. *Br J Surg* 1978; 65: 337-41.
076. Yang CY, Chang-Chien CS, Liaw YF. Controlled trial of protease inhibitor gabexelate mesilate (FOY) in the treatment of acute pancreatitis. *Pancreas* 1987; 2: 698-700.
077. Goebell H. Multicenter double-blind study of gabexate-mesilate (Foy), given intravenously in low dose in acute pancreatitis. *Digestion* 1988; 40: 83 (abstract).
078. Büchler M, Malfertheiner P, Uhl W, Schölmerich J, Stöckmann F, Adler G, Gaus W, Rolle K, Beger HG, German Pancreatitis Study Group. Gabexate mesilate in human acute pancreatitis. *Gastroenterology* 1993; 104: 1165-70.
079. Messori A, Rampazzo R, Scroccaro G, Olivato R, Bassi C, Falconi M, Pederzoli P, Martini N. Effectiveness of gabexate mesilate in acute pancreatitis. A meta-analysis. *Dig Dis Sci* 1995; 40: 734-8.
080. Kontinen YP. Epsilon-aminocaproic acid in treatment of acute pancreatitis. *Scand J Gastroenterol* 1971; 6: 715-8.
081. Cuschieri A, Wood RAB, Cumming JRG, Meehan SE, Mackie CR. Treatment of acute pancreatitis with fresh frozen plasma. *Br J Surg* 1983; 70: 710-2.
082. Leese T, Holliday M, Heath D, Hall AW, Bell PRF. Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. *Br J Surg* 1987; 74: 907-11.
083. Leese T, Thomas WM, Holliday M, Attard A, Watkins M, Neoptolemos JP, Hall C. A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. *Ann Roy Coll Surg Engl* 1991; 73: 207-14.
084. Mäkelä A, Kuusi T, Schröder T. Inhibition of serum phospholipase-A₂ in acute pancreatitis by pharmacological agents in vitro. *Scand J Clin Lab Invest* 1997; 57: 401-8.
085. Lankisch PG, Koop H, Winckler K, Kunze H, Vogt W. Indomethacin treatment of acute experimental pancreatitis in the rat. *Scand J Gastroenterol* 1978; 13: 629-633.
086. Ebbenhøj N, Friis J, Svendsen LB, Bülow S, Madsen P. Indomethacin treatment of acute pancreatitis. A controlled double-blind trial. *Scand J Gastroenterol* 1985; 20: 798-800.
087. Lankisch PG. Treatment of acute pancreatitis: an attempted historical review. *Pancreatology* 2010; 10: 134-41.
088. Fernández-Zapico ME. 'Not knowing something is normally a milestone on the way to knowledge'. An interview with Joan M. Braganza. *Pancreatology* 2009; 9: 717-27.
089. Fernández-Zapico ME. Modeling a scientific career: an essential component of the mentorship process. An interview with John A Williams, professor of molecular and integrative physiology, University of Michigan, Ann Arbor, Mich., USA. *Pancreatology* 2010; 10: 1-3.
090. Blaine SA, Ray KC, Anunobi R, Gannon MA, Washington MK, Means AL. Adult pancreatic acinar cells give rise to ducts but not endocrine cells in response to growth factor signaling. *Development* 2010; 137: 2289-96.
091. Rovira M, Scott SG, Liss AS, Jensen J, Thayer SP, Leach SD. Isolation and characterization of centroacinar/terminal ductal progenitor cells in adult mouse pancreas. *Proc Natl Acad Sci USA* 2010; 107: 75-80.
092. Blaine SA, Ray KC, Anunobi R, Gannon MA, Washington MK, Means AL. Adult pancreatic acinar cells give rise to ducts but not endocrine cells in response to growth factor signaling. *Development* 2010; 137: 2289-96.

093. García-Suárez O, Calavia MG, Pérez-Moltó FJ, Alvarez-Abad C, Pérez-Piñera P, Cobo JM, Vega JA. Immunohistochemical profile of human pancreatic pacinian corpuscles. *Pancreas* 2010; 39: 403-10.
094. Hac SA, Dobosz M, Nalecz A, Reszetow J, Dobrowolski S, Friess H, Michaljevic AL, Mroczkowski P, Studniarek M, Sledzinski Z. Surgical morphology of the pancreatic isthmus. *Pancreatology* 2010; 10: 179-85.
095. Mirilas P, Skandalakis JE. Surgical anatomy of the retroperitoneal spaces part II: the architecture of the retroperitoneal space. *Am Surg* 2010; 76: 33-42.
096. Rajnakova A, Mutignani M, Costamagna G. Wirsung duct duplication. *Pancreas* 2010; 39: 266-8 (letter).
097. Jin ZW, Yu HC, Cho BH, Kim HT, Kimura W, Fujimiya M, Murakami G. Fetal topographical anatomy of the pancreatic head and duodenum with special reference to courses of the pancreaticoduodenal arteries. *Yonsei Med J* 2010; 51: 398-406.
098. Okahara M, Mori H, Kiyosue H, Yamada Y, Sagara Y, Matsumoto S. Arterial supply to the pancreas; variations and cross-sectional anatomy. *Abdom Imaging* 2010; 35: 134-42.
099. Perwaiz A, Singh A, Singh T, Chaudhary A. Incidence and management of arterial anomalies in patients undergoing pancreaticoduodenectomy. *JOP* 2010; 11: 25-30.
100. Hongo N, Mori H, Matsumoto S, Okino Y, Ueda S, Shuto R. Anatomical variations of peripancreatic veins and their intrapancreatic tributaries: multidetector-row CT scanning. *Abdom Imaging* 2010; 35: 143-53.
101. Sakaguchi T, Suzuki S, Morita Y, Oishi K, Suzuki A, Fukumoto K, Inaba K, Kamiya K, Ota M, Setoguchi T, Takehara Y, Nasu H, Nakamura S, Konno H. Analysis of anatomic variants of mesenteric veins by 3-dimensional portography using multidetector-row computed tomography. *Am J Surg* 2010; 200: 15-22.
102. Song SY, Chung JW, Yin YH, Jae HJ, Kim HC, Jeon UB, Cho BH, So YH, Park JH. Celiac axis and common hepatic artery variations in 5002 patients: systematic analysis with spiral CT and DSA. *Radiology* 2010; 255: 278-88.
103. Ziegler M, Al-Haddad M, Schmidt CM. Prepancreatic portal vein in a patient with intestinal nonrotation: report of a case. *J Gastrointest Surg* 2010; 14: 729-31.
104. Joseph P, Raju RS, Vyas FL, Eapen A, Sitaram V. Portal annular pancreas. A rare variant and a new classification. *JOP* 2010; 11: 453-5.
105. Mrak K, Eberl T, Tschmelitsch J, Langner C. Heterotopic pancreatic tissue in the cystic duct: complicating factor or coexisting pathology. *South Med J* 2010; 103: 471-3.
106. Fayoumi S, Al-Husseini L, Jalil R, Abbasi S. Ectopic pancreatic tissue in the thoracic cavity: report of two cases. *Ann Thorac Surg* 2010; 90: e25-7.
107. Chuang MT, Tsai KB, Ma CJ, Hsieh TJ. Ileoileal intussusception due to ileal ectopic pancreas with abundant fat tissue mimicking lipoma. *Am J Surg* 2010; 200: e25-7.
108. Sinha A, Saluja SS, Gamanagatti S. Gastric duplication cyst with macroscopic serosal heterotopic pancreas. *JOP* 2010; 11: 470-3.
109. Shiwani MH. Laparoscopic excision of heterotopic pancreas of stomach. *J Coll Physicians Surg Pak* 2010; 20: 620-1.
110. Goodarzi M, Rashid A, Maru D. Invasive ductal adenocarcinoma arising from pancreatic heterotopia in rectum: case report and review of literature. *Hum Pathol* 2010; 41: 1809-13.

111. Wang XY, Diamant NE, Huizinga JD. Interstitial cells of Cajal. Pacemaker cells of the pancreatic duct? *Pancreas* 2011; 40: 109-13.
112. Park HW, Nam JH, Kim JY, Namkung W, Yoon JS, Lee JS, Kim KS, Venglovecz V, Gray MA, Kim KH, Lee MG. Dynamic regulation of CFTR bicarbonate permeability by [Cl⁻]_i and its role in pancreatic bicarbonate secretion. *Gastroenterology* 2010; 139: 620-31.
113. Barreto SG, Carati CJ, Toouli J, Saccone GT. The islet-acinar axis of the pancreas: more than just insulin. *Am J Physiol Gastrointest Liver Physiol* 2010; 299: G10-22.
114. Barreto SG, Carati CJ, Toouli J, Saccone GT. The islet-acinar axis of the pancreas: more than just insulin. *Am J Physiol Gastrointest Liver Physiol* 2010; 299: G10-22.
115. Itkonen O. Human trypsinogens in the pancreas and in cancer. *Scand J Clin Lab Invest* 2010; 70: 136-43.
116. Lamberk G. The extracellular matrix and cell migration. *Pancreatology* 2010; 10: 4-5.
117. van Geenen EJM, Smits MM, Schreuder TCMA, van der Peet DL, Bloemena E, Mulder CJJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. *Pancreas* 2011; 39: 1185-90.
118. Cordner AP, Armstrong PJ, Newman SJ, Novo R, Sharkey LC, Jessen Emeritus C. Effect of pancreatic tissue sampling on serum pancreatic enzyme levels in clinically healthy dogs. *J Vet Diagn Invest* 2010; 22: 702-7.
119. Lin Y, Sun Z. Current views on type 2 diabetes. *J Endocrinology* 2010; 204: 1-11.
120. Bosi E. Time for testing incretin therapies in early type 1 diabetes? *J Clin Endocrinol Metab* 2010; 95: 2607-9.
121. Brubaker PL. Minireview: update on incretin biology: focus on glucagon-like peptide-1. *Endocrinology* 2010; 151: 1984-9.
122. Ball CG, Correa-Gallego C, Howard TJ, Zyromski NJ, House MG, Pitt HA, Nakeeb A, Schmidt CM, Akisik F, Lillemoie KD. Radiation dose from computed tomography in patients with necrotizing pancreatitis: how much is too much? *J Gastrointest Surg* 2010 Sep 8 [Epub ahead of print].
123. Hawes RH. The evolution of endoscopic ultrasound: improved imaging, higher accuracy for fine needle aspiration and the reality of endoscopic ultrasound-guided interventions. *Curr Opin Gastroenterol* 2010; 26: 436-44.
124. Choi CW, Kim GH, Kang DH, Kim HW, Kim DU, Heo J, Song GA, Park do Y, Kim S. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. *World J Gastroenterol* 2010; 16: 4329-34.
125. Freeman JS. A physiologic and pharmacological basis for implementation of incretin hormones in the treatment of type 2 diabetes mellitus. *Mayo Clin Proc* 2010; 85 Suppl 12: S5-14.
126. Goertz RS, Janka R, Nägel A, Strobel D. Eosinophilic infiltration of the liver and pancreas mimicking metastatic disease. *Z Gastroenterol* 2010; 48: 1138-40.
127. Collins JM, Silva AC, Hayman LA. Arterial anatomy of the pancreas: part 1. Coronal. *J Comput Assist Tomogr* 2010; 34: 633-6.
128. Sandrasegaran K, Lin C, Akisik FM, Tann M. State-of-the-art pancreatic MRI. *Am J Roentgenol* 2010; 195: 42-53.
129. Naish JH, Hutchinson CE, Cauce A, Roberts C, Waterton JC, Hockings PD, Taylor CJ, Parker GJ. Multiple-bolus dynamic contrast-enhanced MRI in the pancreas during a glucose challenge. *J Magn Reson Imaging* 2010; 32: 622-8.

130. Maccioni F, Martinelli M, Al Ansari N, Kagarmanova A, De Marco V, Zippi M, Marini M. Magnetic resonance cholangiography: past, present and future: a review. *Eur Rev Med Pharmacol Sci* 2010; 14: 721-5.
131. Tatli S, Gerbaudo VH, Mamede M, Tuncali K, Shyn PB, Silverman SG. Abdominal masses sampled at PET/CT-guided percutaneous biopsy: initial experience with registration of prior PET/CT images. *Radiology* 2010; 256: 305-11.
132. Schellenberg D, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, Fisher GA, Goodman KA, Koong AC, Chang DT. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; 77: 1420-5.
133. Coté GA, Sherman S. Advances in pancreatobiliary endoscopy. *Curr Opin Gastroenterol* 2010; 26: 429-35.
134. Lawrence C, Stefan AM, Howell DA. Endoscopic appearance of the minor papilla predicts findings at pancreatography. *Dig Dis Sci* 2010; 55: 2412-6.
135. Pata C, Akyüz U, Erzin Y, Mutlu N, Mercan A, Dirican A. Post-procedure elevated amylase and lipase levels after double-balloon enteroscopy: relations with the double-balloon technique. *Dig Dis Sci* 2010; 55: 1982-8.
136. Kerr SE, Kahaleh M, LeGallo RD, Stelow EB. Death after endoscopic retrograde cholangiopancreatography: findings at autopsy. *Hum Pathol* 2010; 41: 1138-44-
137. Chennat J, Waxman I. Initial performance profile of a new 6F self-expanding metal stent for palliation of malignant hilar biliary obstruction. *Gastrointest Endosc* 2010; 72: 632-6.
138. Ridditid W, Rerknimitr R, Janchai A, Kongkam P, Treeprasertsuk S, Kullavanijaya P. Outcome of second interventions for occluded metallic stents in patients with malignant biliary obstruction. *Surg Endosc* 2010; 24: 2216-20.
139. Anderson MA, Brenner DE, Scheiman JM, Simeone DM, Singh N, Sikora MJ, Zhao L, Mertens AN, Rae JM. Reliable gene expression measurements from fine needle aspirates of pancreatic tumors: effect of amplicon length and quality assessment. *J Mol Diagn* 2010; 12: 566-75.
140. Khaliq A, Dutta U, Kochhar R, Singh K. Management of acute pancreatitis: "PANCREAS" contains eight easy steps to remember the treatment. *JOP* 2010; 11: 492-3.
141. Loveday BP, Srinivasa S, Vather R, Mittal A, Petrov MS, Phillips AR, Windsor JA. High quantity and variable quality of guidelines for acute pancreatitis: a systematic review. *Am J Gastroenterol* 2010; 105: 1466-76.
142. Pezzilli R, Zerbi A, Di Carlo V, Bassi C, Delle Fave GF, and the Working Group of the Italian Association for the Study of the Pancreas on Acute Pancreatitis. Practical guidelines for acute pancreatitis. *Pancreatology* 2010; 10: 523-35.
143. Gonzalez-Perez A, Schlienger RG, García Rodríguez LA. Acute pancreatitis in association with type 2 diabetes and anti-diabetic drugs: a population-based cohort study. *Diabetes Care* 2010 Sep 10 [Epub ahead of print].
144. Shen HN, Lu CL. Incidence, resource use, and outcome of acute pancreatitis with/without intensive care. A nationwide population based study in Taiwan. *Pancreas* 2011; 40: 25-9.
145. Oiva J, Mustonen H, Kylänpää ML, Kyhälä L, Alanära T, Aittomäki S, Siitonen S, Kemppainen E, Puolakkainen P, Repo H. Patients with acute pancreatitis complicated by organ failure show highly aberrant monocyte signaling profiles assessed by phospho-specific flow cytometry. *Crit Care* 2010; 38: 1702-8.
146. Cavestro GM, Zuppardo RA, Bertolini S, Sereni G, Frulloni L, Okolicsanyi S, Calzolari C, Singh SK, Sianesi M, Del Rio P, Leandro G, Franzè A, Di Mario F. Connections between genetics and

clinical data: Role of MCP-1, CFTR, and SPINK-1 in the setting of acute, acute recurrent, and chronic pancreatitis. *Am J Gastroenterol* 2010; 105: 199-206.

147. Aoun E, Muddana V, Papachristou GI, Whitcomb DC. SPINK1 N34S is strongly associated with recurrent acute pancreatitis but is not a risk factor for the first or sentinel acute pancreatitis event. *Am J Gastroenterol* 2010; 105: 446-51.

148. Ozhan G, Yanar TH, Ertekin C, Alpertunga B. The effect of genetic polymorphisms of cyclooxygenase 2 on acute pancreatitis in Turkey. *Pancreas* 2010; 39: 371-6.

149. Hyvönen MT, Sinervirta R, Keinänen TA, Fashe T, Grigorenko N, Khomutov AR, Vepsäläinen J, Alhonen L. Acute pancreatitis induced by activated polyamine catabolism is associated with coagulopathy: effects of alpha-methylated polyamine analogs on hemostasis. *Pancreatol* 2010; 10: 208-21.

150. Sonavane A, Baradkar V, Salunkhe P, D'Souza D, Kumar S. Acute necrotizing pancreatitis with pancreatic abscess due to *Prevotella* species in a diabetic. *Indian J Med Microbiol* 2010; 28: 64-7.

151. Trout AT, Elsayes KM, Ellis JH, Francis IR. Imaging of acute pancreatitis: prognostic value of computed tomographic findings. *J Comput Assist Tomogr* 2010; 34: 485-95.

152. Spanier BWM, Nio Y, van der Hulst RWM, Tuynman HARE, Dijkgraaf MGW, Bruno MJ, on behalf of the other members of the EARL study group Practice and yield of early CT scan in acute pancreatitis: a Dutch observational multicenter study. *Pancreatol* 2010; 10: 222-8.

153. Andersen AM, Novovic S, Ersboll AK, Jörgensen LN, Hansen MB. Urinary trypsinogen-2 dipstick in acute pancreatitis. *Pancreas* 2010; 39: 26-30.

154. Chakraborty S, Kaur S, Muddana V, Sharma N, Wittel UA, Papachristou GI, Whitcomb D, Brand RE, Batra SK. Elevated serum neutrophil gelatinase-associated lipocalin is an early predictor of severity and outcome in acute pancreatitis. *Am J Gastroenterol* 2010; 105: 2020-9

155. Chauhan S, Forsmark CE. The difficulty in predicting outcome in acute pancreatitis. *Am J Gastroenterol* 2010; 105: 443-5.

156. Pongprasobchai S, Jianjaronwong V, Charatcharoenwithaya P, Komoltri C, Tanwandee T, Leelakusolvong S, Pausawasdi N, Srikureja W, Chainuvati S, Prachayakul V, Manatsathit S, Kachintorn U. Erythrocyte sedimentation rate and C-reactive protein for the prediction of severity of acute pancreatitis. *Pancreas* 2010; 39: 1226-30.

157. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol* 2010; 105: 435-41.

158. de-Madaria E, Soler-Sala G, Lopez-Font I, Zapater P, Martínez J, Gómez-Escolar L, Sánchez-Fortún C, Sempere L, Pérez-López J, Lluís F, Pérez-Mateo M. Update of the Atlanta classification of severity of acute pancreatitis: should a moderate category be included? *Pancreatol* 2010; 10: 613-9.

159. Imamura Y, Hirota M, Ida S, Hayashi N, Watanabe M, Takamori H, Awai K, Baba H. Significance of renal rim grade on computed tomography in severity evaluation of acute pancreatitis. *Pancreas* 2010; 39: 41-6.

160. Wang X, Zhang J, Li H, Zhang D, Miao B, Cui YF, Zhao EP, Li ZL, Cui NQ. Early predictive factors of inhospital mortality in patients with severe acute pancreatitis. *Pancreas* 2010; 39: 114-5 (letter).

161. Mason JM, Babu BI, Bagul A, Siriwardena A. The performance of Organ Dysfunction Scores for the early prediction and management of severity in acute pancreatitis: an exploratory phase diagnostic study. *Pancreas* 2010; 39: 1104-8.

162. Tang W, Zhang XM, Xiao B, Zeng NL, Pan HS, Feng ZS, Xu XX. Magnetic resonance imaging versus Acute Physiology And Chronic Health Evaluation II score in predicting the severity of acute pancreatitis. *Eur J Radiol* 2010 Sep 14 [Epub ahead of print].
163. Mason JM, Babu BI, Bagul A, Siriwardena A. The performance of Organ Dysfunction Scores for the early prediction and management of severity in acute pancreatitis: an exploratory phase diagnostic study. *Pancreas* 2010; 39: 1104-8.
164. Babu BI, Siriwardena AK. Functional protein C levels during the early phase of clinical acute pancreatitis. *Pancreas* 2010; 39: 1077-81.
165. Pan LY, Wang XY, Li WQ, Li N, Li JS. The intestinal fatty acid binding protein diagnosing gut dysfunction in acute pancreatitis: a pilot study. *Pancreas* 2010; 39: 633-8.
166. Aoun E, Chen J, Reighard D, Gleeson FC, Whitcomb DC, Papachristou GI. Diagnostic accuracy of interleukin-6 and interleukin-8 in predicting severe acute pancreatitis: a meta-analysis. *Pancreatology* 2009; 9: 777-85.
167. Daniel P, Leśniowski B, Jasińska A, Pietruczuk M, Małecka-Panas E. Usefulness of assessing circulating levels of resistin, ghrelin, and IL-18 in alcoholic acute pancreatitis. *Dig Dis Sci* 2010; 55: 2982-7.
168. Teich N, Aghdassi A, Fischer J, Walz B, Caca K, Wallochny T, von Aretin A, von Boyen G, Gopel S, Ockenga J, Leodolter A, Ruddel J, Weber E, Mayerle J, Lerch M, Mössner J, Schiefke I. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. *Pancreas* 2010; 39: 1088-92.
169. Whitlock TL, Tignor A, Webster EM, Repas K, Conwell D, Banks PA, Wu BU. A scoring system to predict readmission of patients with acute pancreatitis to the hospital within 30 days of discharge. *Clin Gastroenterol Hepatol* 2010 Sep 8 [Epub ahead of print].
170. Whitlock TL, Repas K, Tignor A, Conwell D, Singh V, Banks PA, Wu BU. Early readmission in acute pancreatitis: incidence and risk factors. *Am J Gastroenterol* 2010; 105: 2492-7.
171. Fischer M, Hassan A, Sipe BW, Fogel EL, McHenry L, Sherman S, Watkins JL, Schmidt S, Lazzell-Pannell L, Lehman GA. Endoscopic retrograde cholangiopancreatography and manometry findings in 1,241 idiopathic pancreatitis patients. *Pancreatology* 2010; 10: 444-52.
172. Andrén-Sandberg Å, Mayerle JV, Siriwardena AK, Berry DP, Kirk GR, Lerch MM. An optimal randomized study for pain control in acute pancreatitis. In: Johnson CD, Imrie CW. *Pancreatic disease. Protocol and clinical research*. London: Springer, 2010: 41-9. ISBN 978-84882-117-0.
173. Wilms B, Meffert KS, Schultes B. Procaine infusion for pain treatment of acute pancreatitis: a randomized, placebo-controlled double-blind trial. *Dtsch Med Wochenschr* 2010; 135: 2290-5 (in German).
174. Johnson C, Lévy P. Detection of gallstones in acute pancreatitis: when and how? *Pancreatology* 2010; 10: 27-32.
175. Joo KR, Cha JM, Jung SW, Shin HP, Lee JI, Suh YJ, Joo S, Bang SJ. Case review of impacted bile duct stone at duodenal papilla: detection and endoscopic treatment. *Yonsei Med* 2010; 51: 534-9.
176. Srinivasa S, Sammour T, McEntee B, Davis N, Hill AG. Selective use of magnetic resonance cholangiopancreatography in clinical practice may miss choledocholithiasis in gallstone pancreatitis. *Can J Surg* 2010; 53: 403-7.
177. Chen P, Hu B, Wang C, Kang Y, Jin X, Tang C. Pilot study of urgent endoscopic intervention without fluoroscopy on patients with severe acute biliary pancreatitis in the intensive care unit. *Pancreas* 2010; 39: 398-402.

178. van Geenen EJ, Mulder CJ, van der Peet DL, Fockens P, Bruno MJ. Endoscopic treatment of acute biliary pancreatitis: a national survey among Dutch gastroenterologists. *Scand J Gastroenterol* 2010; 45: 1116-20.
179. Nguyen GC, Boudreau H, Jagannath S. Hospital volume as a predictor for undergoing cholecystectomy after admission for acute biliary pancreatitis. *Pancreas* 2010; 39: e6-10.
180. Horwood J, Akbar F, Davis K, Morgan R. Prospective evaluation of a selective approach to cholangiography for suspected common bile duct stones. *Ann R Coll Surg Engl* 2010; 92: 206-10.
181. Kim BJ, Kang P, Lee JK, Sinn DH, Lee KH, Lee KT, Rhee JC, Lim JH. Are the echogenicities on intraductal ultrasonography really biliary microlithiasis? *Dig Dis Sci* 2010; 55: 836-41.
182. Chong VH, Jalihal A. Endoscopic management of biliary disorders during pregnancy. *Hepatobiliary Pancreatic Dis Int* 2010; 9: 180-5.
183. Taniguchi K, Yamashita A, Mutoh KI. Morphological changes in the endocrine and exocrine pancreas of rats after experimental obstructive jaundice. *J Vet Med Sci* 2010 Sep 15 [Epub ahead of print].
184. Mutignani M, Seerden T, Tringali A, Feisal D, Perri V, Familiari P, Costamagna G. Endoscopic hemostasis with fibrin glue for refractory postsphincterotomy and postpapillectomy bleeding. *Gastrointest Endosc* 2010; 71: 856-60.
185. Harada R, Kawamoto H, Fukatsu H, Kato H, Hirao K, Kurihara N, Mizuno O, Ogawa T, Ishida E, Okada H, Yamamoto K, Yamamoto H. Nonprevention of post-endoscopic retrograde cholangiopancreatographic pancreatitis by pancreatic stent after aspiration of pure pancreatic juice in patients with intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; 39: 340-4.
186. Chen ZB, Liang ZY, Zhang Y, Zhang SY, Zheng SS. Surgical intervention of severe post-ERCP-pancreatitis accompanied with duodenum perforation. *J Zhejiang Univ Sci B* 2010; 11: 17-21.
187. Pezzilli R, Mariani A, Gabrielli A, Morselli-Labate AM, Barassi A. Serum and urine trypsinogen activation peptide in assessing post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* 2010; 39: 108-10 (letter).
188. Brand M, Bizo D, O'Farrell P Jr. Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography. *Cochrane Database Syst Rev* 2010; (10): CD007345.
189. Chen SY, Shi H, Zou Xp, Luo HS. Role of ulinastatin in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: the emperor's new clothes or Aladdin's magic lamp? *Pancreas* 2010; 39: 1231-7.
190. Deng LH, Xue P, Huang L, Yang XO, Wan MH, Xia Q. Binge drinking aggravates the outcomes of first-attack severe acute pancreatitis. *Pancreas* 2010; 39: 149-52.
191. Barreto SG, Jardine D, Phillips P, Bhatia M, Saccone GTPB. Can by-products in country-made alcohols induce acute pancreatitis? *Pancreas* 2010; 39: 1199-1204.
192. Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. *Best Pract res Clin Gastroenterol* 2010; 24: 143-55.
193. Vinklerová I, Procházka M, Procházka V, Urbánek K. Incidence, severity, and etiology of drug-induced acute pancreatitis. *Dig Dis Sci* 2010; 55: 2977-81.
194. Li N, Tieng A, Novak S, Fernandes A, Jalal PK, Akerman M, Sideridis K, Bank S. Effects of medications on post-endoscopic retrograde cholangiopancreatography pancreatitis *Pancreatol* 2010; 10: 238-42.

195. Wargo KA, Allman E, Ibrahim F. A possible case of saw palmetto-induced pancreatitis. *South Med J* 2010; 103: 683-5.
196. Raetz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2010; 32: 554-63.
197. Bracamonte JD, Underhill M, Sarmiento P. Acute pancreatitis associated with lisinopril and olanzapine. *Am J Health Syst Pharm* 2010; 67: 214-6.
198. Ahmad FA, Mahmud S. Acute pancreatitis following orlistat therapy: report of two cases. *JOP* 2010; 11: 61-3.
199. Baudry C, Rebours V, Houillier P, Hammel P, Ruszniewski P, Levy P. Recurrent acute pancreatitis caused by association of a novel mutation of the calcium-sensing receptor gene and a heterozygous mutation of the SPINK1 gene. *Pancreas* 2010; 39: 420-1 (letter).
200. Hovland A, Hardersen R, Mollnes TE, Lappegård KT. Selective whole blood lipoprotein apheresis to prevent pancreatitis in drug refractory hypertriglyceridemia. *JOP* 2010; 11: 467-9.
201. Sørensen MK, Møller-Sørensen H, Svane C, Jensen CH, Lange KH, Tybjaerg-Hansen A. Fatal course of a patient during in vitro fertilisation treatment. *Ugeskr Laeger* 2010; 172: 1537-8 (in Danish).
202. Nicholson JA, Smith D, Scott MH. Nicotine gum causing pancreatitis, a case report. *Pancreas* 2010; 39: 116 (letter).
203. Piton G, Barbot O, Manzon C, Moronval F, Patry C, Navellou JC, Belle E, Capellier G. Acute ischemic pancreatitis following cardiac arrest: a case report. *JOP* 2010; 11: 456-9.
204. Rajani R, Przedlacka A, Saha M, de Belder A. Pancreatitis and the broken heart. *Eur J Emerg Med* 2010; 17: 27-9.
205. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. *J Clin Gastroenterol* 2010; 44: 246-53.
206. Amodio J, Brodsky JE. Pediatric Burkitt lymphoma presenting as acute pancreatitis: MRI characteristics. *Pediatr Radiol* 2010; 40: 770-2.
207. Campos L, Omori C, Lotito A, Jesus A, Porta G, Silva C. Acute pancreatitis in juvenile systemic lupus erythematosus: a manifestation of macrophage activation syndrome? *Luos* 2010 Sep 13 [Epub ahead of print].
208. Yang C, Feng GH, Zhu W, Jia Z, Jia PH, Xin, Fang BA, Zhang XP. Combination of hemofiltration and peritoneal dialysis in the treatment of severe acute pancreatitis. *Pancreas* 2010; 39: 16-9.
209. Gardner TB, Vege SS, Chari ST, Petersen BT, Topazian MD, Clain JE, Pearson RK, Levy MJ, Sarr MG. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatology* 2009; 9: 770-6.
210. Préau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med* 2010; 28: 819-25.
211. Piasek M, Rydzewska G, Milewski J, Olszewski S, Furmanek M, Walecki J, Gabryelewicz A. The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: a randomized controlled study. *Pancreas* 2010; 39: 863-7.
212. Zhu YL, Yuan J, Zhang P, Hu X, He Q, Han F, Chen JH. Adjunctive continuous high-volume hemofiltration in patients with acute severe pancreatitis. A prospective nonrandomized study. *Pancreas* 2011; 40: 103-8.

213. Liu Z, Shen Y, Cui N, Yang J. Clinical observation of immunity for severe acute pancreatitis. *Inflammation* 2010 Sep 15 [Epub ahead of print].
214. Sjöberg Bexelius T, Rodríguez LAG, Lindblad M. Use of angiotensin II receptor blockers and the risk of acute pancreatitis: a nested case-control study. *Pancreatology* 2009; 9: 786-92.
215. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010; 5: CD002941.
216. Schäffler A, Hamer O, Dickopf J, Goetz A, Landfried K, Voelk M, Herfarth H, Kopp A, Büchler C, Schölmerich J, Brünner T. Admission resistin levels predict peripancreatic necrosis and clinical severity in acute pancreatitis. *Am J Gastroenterol* 2010; 105: 2474-84.
217. Vege SS, Fletcher JG, Talukdar R, Sarr MG. Peripancreatic collections in acute pancreatitis: correlation between computerized tomography and operative findings. *World J Gastroenterol* 2010; 16: 4219-6.
218. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010; 139: 813-20.
219. Stamatakis M, Stefanaki C, Kontzoglou K, Stergiopoulos S, Giannopoulos G, Safioleas M. Walled-off pancreatic necrosis. *World J Gastroenterol* 2010; 16: 1707-12.
220. Babu BI, Sheen AJ, Lee SH, O'Shea S, Eddleston JM, Siriwardena AK. Open pancreatic necrosectomy in the multidisciplinary management of postinflammatory necrosis. *Ann Surg* 2010; 251: 783-6.
221. Tarantino I, Traina M, Barresi L, Volpes R, Gridelli B. Transgastric plus transduodenal necrosectomy with temporary metal stents placement for treatment of large pancreatic necrosis. *Pancreas* 2010; 39: 269-70 (letter).
222. Wehrmann T, Martchenko K, Riphaut A. Dual access endoscopic necrosectomy of infected pancreatic necrosis: a case report. *Eur J Gastroenterol Hepatol* 2010; 22: 237-40.
223. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, van Goor H, Schaapherder AF, van Eijck CH, Bollen TL, van Ramshorst B, Nieuwenhuijs VB, Timmer R, Laméris JS, Kruijff PM, Manusama ER, van der Harst E, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, van Leeuwen MS, Buskens E, Gooszen HG; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Eng J Med* 2010; 362: 1491-502.
224. Raraty MG, Halloran CM, Dodd S, Ghaneh P, Connor S, Evans J, Sutton R, Neoptolemos JP. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann Surg* 2010; 251: 787-93.
225. Sakamoto Y, Mashiko K, Matsumoto H, Hara Y, Kutsukata N, Yokota H. "Pipe-organ"-like retroperitoneal drainage in severe necrotizing pancreatitis. *Indian J Gastroenterol* 2010; 29: 34-6.
226. Murage KP, Ball CG, Zyromski NJ, Nakeeb A, Ocampo C, Sandrasegaran K, Howard TJ. Clinical framework to guide operative decision making in disconnected left pancreatic remnant (DLPR) following acute or chronic pancreatitis. *Surgery* 2010; 148: 847-56.
227. Andersson E, Ansari D, Andersson R. Major haemorrhagic complications of acute pancreatitis. *Br J Surg* 2010; 97: 1379-84.
228. Dong Z, Petrov MS, Xu J, Shanbhag S, Windsor JA, Pang S. Peritoneal lavage for severe acute pancreatitis: a systematic review of randomised trials. *World J Surg* 2010; 34: 2103-8.
229. Teich N, Mössner J. Nutrition in acute pancreatitis. *Dtsch Med Wochenschr* 2010; 135: 1979-81 (in German).

230. Oláh A, Romics L Jr. Evidence-based use of enteral nutrition in acute pancreatitis. *Langenbecks Arch Surg* 2010; 395: 309-16.
231. Al Samaraee A, McCallum IJ, Coyne PE, Seymour K. Nutritional strategies in severe acute pancreatitis: a systematic review of the evidence. *Surgeon* 2010; 8: 105-10.
232. Petrov MS, Whelan K. Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. *Br J Nutr* 2010; 103: 1287-95.
233. Wu XM, Ji KQ, Wang HY, Li GF, Zang B, Chen WM. Total enteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. *Pancreas* 2010; 39: 248-51.
234. Al-Bahrani A, Darwish A, Hamza N, Benson J, Eddleston J, Snider RH, Nylen ES, Becker KL, Barclay GR, Ammori BJ. Gut barrier dysfunction in critically ill surgical patients with abdominal compartment syndrome. *Pancreas* 2010; 39: 1064-9.
235. Jörgensen M, Brusgaard K, Gylling Crüger D, Gerdes AM, Schaffalitzky de Muckadell OB. Incidence, etiology and prognosis of first-time acute pancreatitis in young patients: a population-based cohort study. *Pancreatology* 2010; 10: 453-61.
236. Morinvil VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas* 2010; 39: 5-8.
237. Deshpande A, Thomas G, Shun A, Roy G, Stormon M, Gaskin K. Dominant dorsal duct syndrome: a rare cause of acute recurrent pancreatitis in children revisited. *Pancreas* 2010; 39: 97-100.
238. Vanlioglou B, Chua TC. Presentation of mumps infection as acute pancreatitis without parotitis. *Pancreas* 2011; 40: 167.
239. Luigiano C, Ferrara F, Fabbri C, Gherzi S, Bassi M, Polifemo AM, Billi P, Fornelli A, Cinquantini F, D'Imperio N. Primary lymphoma of the common bile duct presenting with acute pancreatitis and cholangitis. *Endoscopy* 2010; 42 Suppl 2: E265-6.
240. Johansen ME, Mattsson N, Larsen ML. Extreme levels of hyperlipidaemia as a cause of acute pancreatitis. *Ugeskr Laeger* 2010; 172: 2768-9 (in Danish).
241. Shin do H, Lee KH, Kim CH, Kim KH, Park SH, Chang DK, Lee JK, Lee KT. A case of inferior vena cava thrombosis and acute pancreatitis in a patient with ulcerative colitis. *Korean J Gastroenterol* 2010; 56: 255-9 (in Korean).
242. Ping C, Yongping Z, Minmin Q, Weiyan Y, Yaozong Y. Activated protein C improves the severity of severe acute pancreatitis via up-regulating the expressions of endothelial cell protein C receptor and thrombomodulin. *Dig Dis Sci* 2010; 55: 1599-609.
243. Machado MCC, Coelho AMM, Martins J, Sampietre S, Molan N, Patzina R, Machado MAC, Jancar S. CO2 abdominal insufflation decreases local and systemic inflammatory response in experimental acute pancreatitis. *Pancreas* 2010; 39: 175-81.
244. Kutluana U, Oruc N, Nart D, Kaptanoglu B, Yonetci N, Ozutemiz O. Leflunomide: is a new oral agent in treatment of acute pancreatitis? *Pancreas* 2010; 39: 237-42.
245. Souza LJ, Coelho AMM, Sampietre SN, Martins JO, Cunha JE, Machado MCC. Antii inflammatory effects of peritoneal lavage in acute pancreatitis. *Pancreas* 2011; 39: 1180-4.
246. Beglinger C. Diagnosis of chronic pancreatitis. *Dig Dis* 2010; 28: 359-63.
247. Milosavljevic T, Kostic Milosavljevic M, Krstic M, Jovanovic I. Classification of chronic pancreatitis. *Dig Dis* 2010; 28:330-3.

248. DiMagno MJ, DiMagno EP. Chronic pancreatitis. *Curr Opin Gastroenterol* 2010; 26: 490-8.
249. Lerch MM, Mayerle J, Aghdassi AA, Budde C, Nitsche C, Sauter G, Persike M, Günther A, Simon P, Weiss FU. Advances in the etiology of chronic pancreatitis. *Dig Dis* 2010; 28: 324-9.
250. Jörgensen M, Brusgaard K, Crüger DG, Gerdes AM, de Muckadell OB. Incidence, prevalence, etiology, and prognosis of first-time chronic pancreatitis in young patients: a nationwide cohort study. *Dig Dis Sci* 2010; 55: 2988-98.
251. Nøjgaard C, Bendtsen F, Becker U, Andersen JR, Holst C, Matzen P. Danish patients with chronic pancreatitis have a four-fold higher mortality rate than the Danish population. *Clin Gastroenterol Hepatol* 2010; 8: 384-90.
252. Law R, Parsi M, Lopez R, Zuccaro G, Stevens T. Cigarette smoking is independently associated with chronic pancreatitis. *Pancreatol* 2010; 10: 54-9.
253. Andriulli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve PE. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. *Pancreas* 2010; 39: 1205-10.
254. Ammann RW, Raimondi S, Maisonneuve P, Mullhaupt B, Zurich Pancreatitis Study Group. Is obesity an additional risk factor for alcoholic chronic pancreatitis? *Pancreatol* 2010; 10: 47-53.
255. Petrov MS. Therapeutic implications of oxidative stress in acute and chronic pancreatitis. *Curr Opin Clin Nutr Metab Care* 2010; 13: 562-8.
256. Arumugam G, Padmanaban M, Krishnan D, Panneerselvam S, Rajagopal S. Influence of copper, iron, zinc and Fe³⁺ haemoglobin levels on the etiopathogenesis of chronic calcific pancreatitis – a study in patients with pancreatitis. *Biol Trace Elem res* 2010 Sep 1 [Epub ahead of print].
257. Ozhan G, Yanar HT, Ertekin C, Alpertunga B. Polymorphisms in tumour necrosis factor alpha (TNFalpha) gene in patients with acute pancreatitis. *Mediators Inflamm* 2010 Apr 14 [Epub ahead of print].
258. Pelletier AL, Bienvenu T, Rebours V, O'Toole D, Hentic O, Maire F, Hammel P, Ruszniewski P, Lévy P. CFTR gene mutation in patients with apparently idiopathic pancreatitis: lack of phenotype-genotype correlation. *Pancreatol* 2010; 10: 158-64.
259. de Cid R, Ramos MD, Aparisi L, Garcia C, Mora J, Estivill X, Farre A, Casals T. Independent contribution of common CFTR variants to chronic pancreatitis. *Pancreas* 2010; 39: 209-15.
260. Midha S, Khajuria R, Shastri S, Kabra M, Garg PK. Idiopathic chronic pancreatitis in India: phenotypic characterisation and strong genetic susceptibility due to SPINK1 and CFTR gene mutations. *Gut* 2010; 59: 800-7.
261. Rosendahl J, Teich N, Kovacs P, Szmola R, Blüher M, Gress TM, Hoffmeister A, Keim V, Löhr M, Mössner J, Nickel R, Ockenga J, Pfützer R, Schulz HU, Stumvoll M, Wittenburg H, Sahin-Tóth M, Witt H. Complete analysis of the human mesotrypsinogen gene (PRSS3) in patients with chronic pancreatitis. *Pancreatol* 2010; 10: 243-9.
262. Muddana V, Park J, Lamb J, Yadav D, Papachristou G, Hawes RH, Brand R, Slivka A, Whitcomb DC. Are genetic variants in the platelet-derived growth factor-beta gene associated with chronic pancreatitis? *Pancreas* 2010; 39: 1215-9.
263. Witt H, Rosendahl J, te Morsche RHM, Santhosh S, Chacko A, Schulz HU, Landt O, Teich N, Keim V, Mössner J, Gress TM, Ockenga J, Schmidt H, Kovacs P, Blüher M, Stumvoll M, Kage A, Groneberg DA, Jansen JBMJ, Nickel R, Drenth J. Mutational analysis of the gene encoding the zymogen granule membrane glycoprotein 2 (GP2) in patients with chronic pancreatitis. *Pancreas* 2010; 39: 188-92.

264. Masson E, Paliwal S, Bhaskar S, Prakash S, Scotet V, Reddy DN, Le Marechal C, Ratan Chandak G, Chen JM, Ferec C. Genetic analysis of the glycoprotein 2 gene in patients with chronic pancreatitis. *Pancreas* 2010; 39: 353-8.
265. Schmitz-Winnenthal H, Pietsch DH, Schimmack S, Bonertz A, Udonta F, Ge Y, Galindo L, Specht S, Volk C, Zraggen K, Koch M, Büchler MW, Weitz J, Beckhove P. Chronic pancreatitis is associated with disease-specific regulatory T-cell responses. *Gastroenterology* 2010; 138: 1178-88.
266. Zuccaro P, Stevens T, Repas K, Diamond R, Lopez R, Wu B, Conwell DL. Magnetic resonance cholangiopancreatography reports in the evaluation of chronic pancreatitis: a need for quality improvement. *Pancreatology* 2009; 9: 764-9.
267. Seicean A. Endoscopic ultrasound in chronic pancreatitis: where are we now? *World J Gastroenterol* 2010; 16: 4253-63.
268. Petrone MC, Arcidiacono PG, Perri F, Carrara S, Boemo C, Testoni PA. Chronic pancreatitis-like changes detected by endoscopic ultrasound in subjects without signs of pancreatic disease: do these indicate age-related changes, effects of xenobiotics, or early chronic pancreatitis? *Pancreatology* 2010; 10: 597-602.
269. Braden B. ¹³C Breath tests for the assessment of exocrine pancreatic function. *Pancreas* 2010; 39: 955-9.
270. Braden B. ¹³C Breath tests for the assessment of exocrine pancreatic function. *Pancreas* 2010; 39: 955-9.
271. Albashir S, Bronner MP, Parsi MA, Walsh RM, Stevens T. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. *Am J Gastroenterol* 2010; 105: 2498-503.
272. Stevens T, Dumot JA, Parsi MA, Zuccaro G, Vargo JJ. Combined endoscopic ultrasound and secretin endoscopic pancreatic function test in patients evaluated for chronic pancreatitis. *Dig Dis Sci* 2010; 55: 2681-7.
273. Baumgart M, Werther M, Bockholt A, Scheurer M, Ruschoff J, Dietmaier W, Ghadimi BM, Heinmoller E. Genomic instability at both the base pair level and the chromosomal level is detectable in earliest PanIN lesions in tissues of chronic pancreatitis. *Pancreas* 2010; 39: 1093-103.
274. Uguz A, Yakan S, Gurcu B, Yilmaz F, Ilter T, Coker A. Xanthogranulomatous pancreatitis treated by duodenum-preserving pancreatic head resection. *Hepatobiliary Pancreat Dis Int* 2010; 9: 216-8.
275. Said HM, Mee L, Sekar VT, Ashokkumar B, Pandol SJ. Mechanism and regulation of folate uptake by pancreatic acinar cells: effect of chronic alcohol consumption. *Am J Physiol Gastrointest Liver Physiol* 2010; 298: G985-93.
276. Maruyama K, Harada S, Yokoyama A, Mizukami S, Naruse S, Hirota M, Nishimori I, Otsuki M. Association analyses of genetic polymorphisms of GSTM1, GSTT1, NQO1, NAT2, LPL, PRSS1, PSTI, and CFTR with chronic alcoholic pancreatitis in Japan. *Alcohol Clin Exp Res* 2010; 34 suppl 1: S34-8.
277. Navaneethan U, Shen B. Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. *Inflamm Bowel Dis* 2010; 16: 1598-619.
278. Ito T, Otsuki M, Igarashi H, Kihara Y, Kawabe K, Nakamura T, Fujimori N, Oono T, Takayanagi R, Shimosegawa T. Epidemiological study of pancreatic diabetes in Japan in 2005: a nationwide study. *Pancreas* 2010; 39: 829-35.
279. Rosa-E-Silva L, Troncon LE, Gallo L Jr, Foss MC, Passos AD, Perdoná GC, Achcar JA, Oliveira RB. Determinants of accelerated small intestinal transit in alcohol-related chronic pancreatitis. *Dig Dis Sci* 2010; 55: 1017-25.

280. Hornum M, Pedersen JF, Larsen S, Olsen O, Holst JJ, Knop FK. Increased postprandial response of glucagon-like peptide-2 in patients with chronic pancreatitis and pancreatic exocrine insufficiency. *Pancreatology* 2010; 10: 201-7.
281. Rieder S, Michalski CW, Friess H. Indications for endoscopic or surgical treatment of chronic pancreatitis. *Dig Dis* 2010; 28: 344-9.
282. Ansari D, Andersson E, Andersson B, Andersson R. Chronic pancreatitis: potential future interventions. *Scand J Gastroenterol* 2010; 45: 1022-8.
283. Andersen DK, Frey CF. The evolution of the surgical treatment of chronic pancreatitis. *Ann Surg* 2010; 251: 18-32.
284. Chirletti P, Peparini N, Caronna R, Fanello G, Delogu G, Meniconi RL. Roux-en-Y end-to-end and end-to-side double pancreaticojejunostomy: application of the reconstructive method of the Beger procedure to central pancreatectomy. *Langenbecks Arch Surg* 2010; 395: 89-93.
285. Farkas G, Leindler L, Daroczi M, Farkas G Jr. Ten-year experience with duodenum and organ-preserving pancreatic head resection (Büchler-Farkas modification) in the surgical treatment of chronic pancreatitis. *Pancreas* 2010; 39: 1082-7.
286. Negi S, Singh A, Chaudhary A. Pain relief after Frey's procedure for chronic pancreatitis. *Br J Surg* 2010; 97: 1087-95.
287. Miccini M, Amore Bonapasta S, Gregori M, Bononi M, Fornasari V, Tocchi A. Indications and results for transduodenal sphincteroplasty in the era of endoscopic sphincterotomy. *Am J Surg* 2010; 200: 247-51.
288. Sutton JM, Schmulewitz N, Sussman JJ, Smith M, Kurland JE, Brunner JE, Salehi M, Choe KA, Ahmad SA. Total pancreatectomy and islet cell autotransplantation as a means of treating patients with genetically linked pancreatitis. *Surgery* 2010; 148: 676-85.
289. Takita M, Naziruddin B, Matsumoto S, Noguchi H, Shimoda M, Chujo D, Itoh T, Sugimoto K, Onaca N, Lamont J, Lara LF, Levy ML. Implication of pancreatic image findings in total pancreatectomy with islet autotransplantation for chronic pancreatitis. *Pancreas* 2011; 40: 67-71
290. Kobayashi T, Manivel J, Bellin MD, Carlson A, Moran A, Freeman ML, Hering BJ, Sutherland DER. Correlation of pancreatic histopathologic findings and islet yield in children with chronic pancreatitis undergoing total pancreatectomy and islet autotransplantation. *Pancreas* 2010; 39: 57-63.
291. Parsi MA, Stevens T, Lopez R, Vargo JJ. Extracorporeal shock wave lithotripsy for prevention of recurrent pancreatitis caused by obstructive pancreatic stones. *Pancreas* 2010; 39: 153-5.
292. King JC, Reber HA, Shiraga S, Hines OJ. Pancreatic-pleural fistula is best managed by early operative intervention. *Surgery* 2010; 147: 154-9.
293. Hammer HF. Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes. *Dig Dis* 2010; 28: 339-43.
294. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, Sander-Struckmeier S, Caras S. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. *Am J Gastroenterol* 2010; 105: 2276-86.
295. Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K, Bennett D. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. *Clin Ther* 2010; 32: 89-103.

296. Fregni F, Potvin K, Dasilva D, Wang X, Lenkinski RE, Freedman SD, Pascual-Leone A. Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain. *Eur J Pain* 2010 Sep 3 [Epub ahead of print].
297. Joseph S, Li G, Lindholm E, Zhou Y, Go VLW, Vinik AI, O'Dorisio TM, Mamikunian G, Woltering EA. A prospective trial on the effect of body mass index and sex on plasma octreotide levels in patients undergoing long-term octreotide LAR therapy. *Pancreas* 2010; 39: 964-6.
298. Joseph S, Li G, Lindholm E, Zhou Y, Go VLW, Vinik AI, O'Dorisio TM, Mamikunian G, Woltering EA. A prospective trial on the effect of body mass index and gender on plasma octreotide levels in patients undergoing long term therapy with octreotide LAR. *Pancreas* 2010; 39: 273-4 (letter).
299. Boyd AE, Leary CC, Brook JP, Boving VG, Dagohoy CG, DeFord LL, Garris JL, Mares JE, Phan AT, Yao JC. Gluteal intramuscular injections: techniques associated with successful octreotide LAR injection. *Pancreas* 2010; 39: 271-2 (letter).
300. Garris JL, DeFord LL, Dagohoy CG, Leary CC, Boving VG, Brook JP, Mares JE, Boyd AE, Phan A, Yao JC. Gender related issues in gluteal intramuscular injections. *Pancreas* 2010; 39: 273 (letter).
301. Mares JE, Dagohoy CG, Leary CC, DeFord LL, Boving VG, Brook JP, Garris JL, Boyd AE, Phan AT, Yao JC. Gluteal intramuscular injections: CT evaluation of factors associated with success and failure. *Pancreas* 2010; 39: 275 (letter).
302. Mokrowiecka A, Pinkowski D, Malecka-Panas E, Johnson CD. Clinical, emotional and social factors associated with quality of life in chronic pancreatitis. *Pancreatology* 2010; 10: 39-46.
303. van Loo ES, van Baal MC, Gooszen HG, Ploeg RJ, Nieuwenhuijs VB. Long-term quality of life after surgery for chronic pancreatitis. *Br J Surg* 2010; 97: 1079-86.
304. Zhang W, Gao J, Zhao T, Wu WB, Bai Y, Zou DW, Li ZS. High-dose naproxen aggravates pancreatic fibrosis in a rat model of chronic pancreatitis. *Pancreas* 2010; 39: 293-300.
305. Shinozaki S, Mashima H, Ohnishi H, Sugano K. IL-13 promotes the proliferation of rat pancreatic stellate cells through the suppression of NF-kappaB/TGF-beta1 pathway. *Biochem Biophys Res Commun* 2010; 393: 61-5.
306. Masamune A, Satoh A, Watanabe T, Kikuta K, Satoh M, Suzuki N, Satoh K, Shimosegawa T. Effects of ethanol and its metabolites on human pancreatic stellate cells. *Dig Dis Sci* 2010; 55: 204-11.
307. Nishida A, Andoh A, Imaeda H, Inatomi O, Shiomi H, Fujiyama Y. Expression of interleukin 1-like cytokine interleukin 33 and its receptor complex (ST2L and IL1RAcP) in human pancreatic myofibroblasts. *Gut* 2010; 59: 531-41.
308. Berna MJ, Seiz O, Nast JF, Benten D, Blaeker M, Koch J, Lohse AW, Pace A. CCK1 and CCK-2-receptors are expressed on pancreatic stellate cells and induce collagen production. *J Biol Chem* 2010 Sep 14 [Epub ahead of print].
309. Morishita K, Shimizu K, Haruta I, Kawamura S, Kobayashi M, Shiratori K. Engulfment of gram-positive bacteria by pancreatic stellate cells in pancreatic fibrosis. *Pancreas* 2010; 39: 1002-7.
310. Chari ST, Klöppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T, and The Autoimmune Pancreatitis International Cooperative Study Group (APICS). Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu Consensus Document. *Pancreas* 2010; 39: 280-3.
311. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Okumura F, Miyabe K, Yoshida M, Sano H, Takada H, Kanematsu T, Joh T. Comparative evaluation of the Japanese diagnostic criteria for autoimmune pancreatitis. *Pancreas* 2010; 39: 1173-9.
312. Dhall D, Suriawinata AA, Tang LH, Shia J, Klimstra DS. Use of immunohistochemistry for IgG4 in the distinction of autoimmune pancreatitis from peritumoral pancreatitis. *Hum Pathol* 2010; 41: 643-52.

313. Narula N, Vasudev M, Marshall JK. IgG₄-related sclerosing disease: a novel mimic of inflammatory bowel disease. *Dig Dis Sci* 2010; 55: 3047-51.
314. Lim EJ, Bhathal PS, Tagkalidis PP, Speer AG. Catching a chameleon: IgG4-related systemic disease. *Med J Austr* 2010; 193: 418-20.
315. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010; 34: 1812-9.
316. Novotný I, Díte P, Lata J, Nechutová H, Kianicka B. Autoimmune pancreatitis – recent advances. *Dig Dis* 2010; 28: 334-8.
317. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 2010; 17: 303-32.
318. Sugumar A, Chari ST. Diagnosis and treatment of autoimmune pancreatitis. *Curr Opin Gastroenterol* 2010; 26: 513-8.
319. Sah RP, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N, Farnell MB, Vege SS. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010; 139: 140-8.
320. Kamisawa T, Takuma K, Tabata T, Inaba Y, Egawa N, Tsuruta K, Hishima T, Sasaki T, Itoi T. Serum IgG4-negative autoimmune pancreatitis. *J Gastroenterol* 2010 Sep 8 [Epub ahead of print].
321. Farris AB 3rd, Lauwers GY, Deshpande V. Autoimmune pancreatitis-related diabetes: quantitative analysis of endocrine islet cells and inflammatory infiltrate. *Virchows Arch* 2010; 457: 329-36.
322. Uehara T, Hamano H, Kawa S, Sano K, Oki K, Kobayashi Y, Nagaya T, Akamatsu T, Kurozumi M, Fujinaga Y, Tanaka E, Honda T, Ota H. Chronic gastritis in the setting of autoimmune pancreatitis. *Am J Surg Pathol* 2010; 34: 1241-9.
323. Sah RP, Chari ST. Clinical hypothyroidism in autoimmune pancreatitis. *Pancreas* 2010; 39: 1114-6 (letter).
324. Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedures for IgG4-related sclerosing cholangitis. *J Hepatobiliary Pancreat Sci* 2010 Sep 2 [Epub ahead of print].
325. Park SH, Kim MH, Kim SY, Kim HJ, Moon SH, Lee SS, Byun JH, Lee SK, Seo DW, Lee MG. Magnetic resonance cholangiopancreatography for the diagnostic evaluation of autoimmune pancreatitis. *Pancreas* 2010; 39: 1191-8.
326. De Lisi S, Buscarini E, Arcidiacono PG, Petrone M, Menozzi F, Testoni PA, Zambelli A. Endoscopic ultrasonography findings in autoimmune pancreatitis: be aware of the ambiguous features and look for the pivotal ones. *JOP* 2010; 11: 78-84.
327. Kawa S, Okazaki K, Kamisawa T, Shimosegawa T, Tanaka M; Working members of Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: II. Extrapancreatic lesions, differential diagnosis. *J Gastroenterol* 2010; 45: 355-69.
328. Sah RP, Pannala R, Zhang L, Graham RP, Sugumar A, Chari ST. Eosinophilia and allergic disorders in autoimmune pancreatitis. *Am J Gastroenterol* 2010; 105: 2485-91.
329. Pezzilli R, Barassi A, Corsi MM, Morselli-Labate AM, Campana D, Casadei R, Santini D, Corinaldesi R, D'Eril GM. Serum leptin, but not adiponectin and receptor for advanced glycation end products, is able to distinguish autoimmune pancreatitis from both chronic pancreatitis and pancreatic neoplasms. *Scand J Gastroenterol* 2010; 45: 93-9.
330. Song TJ, Kim MH, Moon SH, Eum JB, Park do H, Lee SS, Seo DW, Lee SK. The combined measurement of total serum IgG and IgG4 may increase diagnostic sensitivity for autoimmune

- pancreatitis without sacrificing specificity, compared with IgG4 alone. *Am J Gastroenterol* 2010; 105: 1655-60.
331. Löhr JM, Faissner R, Koczan D, Bewerunge P, Bassi C, Brors B, Eils R, Frulloni L, Funk A, Halangk W, Jesnowski R, Kaderali L, Kleeff J, Krüger B, Lerch MM, Lösel R, Magnani M, Neumaier M, Nittka S, Sahin-Tóth M, Sängler J, Serafini S, Schnölzer M, Thierse HJ, Wandschneider S, Zamboni G, Klöppel G. Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling and immunoassays identify pancreatic enzymes as a major target of the inflammatory process. *Am J Gastroenterol* 2010; 105: 2060-71.
332. Tabata R, Tabata C, Okamoto T, Omori K, Terada M, Nagai T. Autoimmune pancreatitis associated with myelodysplastic syndrome. *Int Arch Allergy Immunol* 2010; 151: 168-72.
333. Kim HM, Chung MJ, Chung JB. Remission and relapse of autoimmune pancreatitis: focusing on corticosteroid treatment. *Pancreas* 2010; 39: 555-60.
334. Frulloni L, Scattolini C, Katsotourchi AM, Amodio A, Gabbrielli A, Zamboni G, Benini L, Vantini I. Exocrine and endocrine pancreatic function in 21 patients suffering from autoimmune pancreatitis before and after steroid treatment. *Pancreatol* 2010; 10: 129-33.
335. Ko SB, Mizuno N, Yatabe Y, Yoshikawa T, Ishiguro H, Yamamoto A, Azuma S, Naruse S, Yamao K, Muallem S, Goto H. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* 2010; 138: 1988-96.
336. Nakazawa T, Naitoh I, Ando T, Hayashi K, Okumura F, Miyabe K, Yoshida M, Ohara H, Joh T. A case of advanced-stage sclerosing cholangitis with autoimmune pancreatitis not responsive to steroid therapy. *JOP* 2010; 11: 58-60.
337. Nishi H, Shibagaki Y, Hirano K, Akahane M, Kido R, Nangaku M, Kaname S, Sasahira N, Isayama H, Tada M, Tsukamoto R, Ohtomo K, Omata M, Fujita T. Laboratory and imaging features of kidney involvement in autoimmune pancreatitis: incidence, correlation, and steroid therapy response. *Lin Nephrol* 2010; 73: 253-9.
338. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, Okumura F, Miyabe K, Yoshida M, Sano H, Takada H, Joh T. Clinical significance of extrapancreatic lesions in autoimmune pancreatitis. *Pancreas* 2010; 39: e1-5.
339. Kubota K, Wada T, Kato S, Mozaki Y, Yoneda M, Fujita K, Takahashi H, Inamori M, Abe Y, Kobayashi N, Kirikoshi H, Saito S, Inayama Y, Nakajima A. Highly active state of autoimmune pancreatitis with Mikulicz disease. *Pancreas* 2010; 39: e6-10.
340. Tomita H, Matsubayashi H, Sasaki K, Takizawa K, Ikehara H, Kakushima N, Tanaka M, Yamaguchi Y, Ono H. A case of autoimmune pancreatitis accompanied with Mikulicz's disease. *Nippon Shokakibyō Gakkai Zasshi* 2010; 107: 775-83 (Japanese).
341. Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, Pilch BZ, Deshpande V. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010; 34: 202-10.
342. Robison LS, Canon CL, Varadarajulu S, Eloubeidi MA, Vickers S, Mel Wilcox C. Autoimmune pancreatitis mimicking pancreatic cancer. *J Hepatobiliary Pancreat Sci* 2010 Sep 2 [Epub ahead of print].
343. Loos M, Esposito I, Hedderich DH, Ludwig L, Fingerle A, Friess H, Klöppel G, Büchler P. Autoimmune pancreatitis complicated by carcinoma of the pancreatobiliary system. A case report and review of the literature. *Pancreas* 2011; 40: 137-43.
344. Hamada Y, Inoue H, Noda T, Aoki M, Katsurahara M, Kosaka R, Tanaka K, Imoto I, Isaji S, Takei Y. A case of IgG4-related sclerosing cholangitis with pancreas divisum. *Nippon Shokakibyō Gakkai Zasshi* 2010; 107: 1184-91 (in Japanese).

345. Triantopoulou C, Malachias G, Maniatis P, Anastopoulos J, Sifas I, Papailiou J. Renal lesions associated with autoimmune pancreatitis: CT findings. *Acta Radiol* 2010; 51: 702-7.
346. Jesnowski R, Isaksson B, Möhrcke C, Bertsch C, Bulajic M, Schneider-Brachert W, Klöppel G, Lowenfels AL, Maisonneuve P, Löhr JM. *Helicobacter pylori* in autoimmune pancreatitis and pancreatic carcinoma. *Pancreatology* 2010; 10: 462-6.
347. Takase M, Imai T, Nozaki F. Relapsing autoimmune pancreatitis in a 14-year-old girl. *J Nippon Med Sch* 2010; 77: 29-34.
348. Jacobs EJ, Chanock SJ, Fuchs CS, Lacroix A, McWilliams RR, Stepilowski E, Stolzenberg-Solomon RZ, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Petersen G, Zheng W, Agalliu I, Allen NE, Amundadottir L, Boutron-Ruault MC, Buring JE, Canzian F, Clipp S, Dorronsoro M, Gaziano JM, Giovannucci EL, Hankinson SE, Hartge P, Hoover RN, Hunter DJ, Jacobs KB, Jenab M, Kraft P, Kooperberg C, Lynch SM, Sund M, Mendelsohn JB, Mouw T, Newton CC, Overvad K, Palli D, Peeters PH, Rajkovic A, Shu XO, Thomas G, Tobias GS, Trichopoulos D, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu K, Zeleniuch-Jacquotte A. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Int J Cancer* 2010; 127: 1421-8.
349. Brune KA, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, Klein AP. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010; 102: 119-26.
350. Shirts BH, Burt RW, Mulvihill SJ, Cannon-Albright LA. A population-based description of familial clustering of pancreatic cancer. *Clin Gastroenterol Hepatol* 2010; 8: 812-6.
351. Slater EP, Langer P, Fendrich V, Habbe N, Chaloupka B, Matthäi E, Sina M, Hahn SA, Bartsch DK. Prevalence of BRCA2 and CDKN2a mutations in German familial pancreatic cancer families. *Fam Cancer* 2010; 9: 335-43.
352. Del Chiaro M, Zerbi A, Capurso G, Zamboni G, Maisonneuve P, Presciuttini S, Arcidiacono PG, Calculli L, Falconi M. Familial pancreatic cancer in Italy. Risk assessment, screening programs and clinical approach: a position paper from the Italian Registry. *Dig Liver Dis* 2010; 42: 597-605.
353. Rosendahl J, Rónai Z, Kovacs P, Teich N, Wittenburg H, Blüher M, Stumvoll M, Mössner J, Keim V, Bradbury ARM, Sahin-Tóth M. Sequence analysis of the human tyrosylprotein sulfotransferase-2 gene in subjects with chronic pancreatitis. *Pancreatology* 2010; 10: 165-72.
354. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010; 105: 1258-64.
355. Goh PG, Moon HS, Sung JK, Jeong HY, Song KS. A case of Peutz-Jeghers syndrome with intraductal papillary mucinous carcinoma of pancreas. *Korean J Gastroenterol* 2010; 55: 73-7 (in Korean).
356. Fiskerstrand T, Houge G, Sund S, Scheie D, Leh S, Boman H, Knappskog PM. Identification of a gene for renal-hepatic-pancreatic dysplasia by microarray-based homozygosity mapping. *J Mol Diagn* 2010; 12: 125-31.
357. Köklü S, Alioğlu B, Akbal E, Koçak E. Celiac disease in siblings with Pearson syndrome. *Am J Med Sci* 2010; 339: 392-4.
358. Linden T, Ehlert K, Niemeyer CM, Fleischhack G, Jürgens H, Rossig C. Molecular diagnosis of Shwachman-Diamond syndrome in a child with incomplete clinical disease phenotype. *Pediatr Blood Cancer* 2010; 55: 177-9.
359. Sorrentino S, Conte M, Nozza P, Granata C, Capra V, Avanzini S, Garaventa A. Simultaneous occurrence of pancreatoblastoma and neuroblastoma in a newborn with Beckwith-Wiedemann syndrome. *J Pediatr Hematol Oncol* 2010; 32: e207-9.

360. Chetty-John S, Piwnica-Worms K, Bryant J, Bernardini I, Fischer RE, Heller T, Gahl WA, Gunay-Aygun M. Fibrocystic disease of liver and pancreas; under-recognized features of the X-linked ciliopathy oral-facial-digital syndrome type 1 (OFD I). *Am J Med Genet A* 2010 Sep 3 [Epub ahead of print].
361. Fajans SS, Bell GI, Paz VP, Below JE, Cox NJ, Martin C, Thomas IH, Chen M. Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the IPF1 mutation Pro63fsX60. *Transl Res* 2010; 156: 7-14.
362. Maurea S, Mollica C, Imbriaco M, Fusari M, Camera L, Salvatore M. Magnetic resonance cholangiography with mangafodipir trisodium in Caroli's disease with pancreas involvement. *JOP* 2010; 11: 460-3.
363. Urushihara N, Fukumoto K, Fukuzawa H, Suzuki K, Matsuoka T, Kawashima S, Watanabe K, Hasegawa S. Recurrent pancreatitis caused by pancreatobiliary anomalies in children with annular pancreas. *J Pediatr Surg* 2010; 45: 741-6.
364. Terui K, Hishiki T, Saito T, Sato Y, Takenouchi A, Saito E, Ono S, Kamata T, Yoshida H. Pancreas divisum in pancreatobiliary maljunction in children. *Pediatr Surg Int* 2010; 26: 419-22.
365. Sequeiros IM, Hester K, Callaway M, Williams A, Garland Z, Powell T, Wong FS, Jarad NA; Bristol Cystic Fibrosis Diabetes Group. MRI appearance of the pancreas in patients with cystic fibrosis: a comparison of pancreas volume in diabetic and non-diabetic patients. *Br J Radiol* 2010; 83: 921-6.
366. Phillips PA, Yang L, Shulkes A, Vonlaufen A, Poljak A, Bustamante S, Warren A, Xu Z, Guilhaus M, Pirola R, Apte MV, Wilson JS.
367. Fujita H, Ohuchida K, Mizumoto K, Nakata K, Yu J, Kayashima T, Cui L, Manabe T, Ohtsuka T, Tanaka M. Alpha-smooth muscle actin expressing stroma promotes an aggressive tumor biology in pancreatic ductal adenocarcinoma. *Pancreas* 2010; 39: 1254-62.
368. Morishita K, Shimizu K, Haruta I, Kawamura S, Kobayashi M, Shiratori K. Engulfment of gram-positive bacteria by pancreatic stellate cells in pancreatic fibrosis. *Pancreas* 2010; 39: 1002-7.
369. Simianu VV, Zyromski NJ, Nakeeb A, Lillemo KD. Pancreatic cancer: progress made. *Acta Oncol* 2010; 49: 407-17.
370. Mortensen MB, Svolgaard B, Odense MV. Diagnosis and assessment of pancreatic cancer. *Ugeskr Laeger* 2010; 172: 1369-72 (in Danish).
371. Bergenfeldt M, Hansen CP, Mortensen MB. Surgical treatment of pancreatic cancer. *Ugeskr Laeger* 2010; 172: 1358-60 (in Danish).
372. Tanaka M. Evidence-based guidelines for the management of pancreatic cancer, version 2009. *Gan To Kagaku Ryoho* 2010; 37: 592-603 (in Japanese).
373. Simons JP, Ng SC, McDade TP, Zhou Z, Earle CC, Tseng JF. Progress for resectable pancreatic cancer?: a population-based assessment of US practices. *Cancer* 2010; 116: 1681-90.
374. Krejs GJ. Pancreatic cancer: epidemiology and risk factors. *Dig Dis* 2010; 28: 355-8.
375. Ellison LF. Measuring the effect of including multiple cancers in survival analyses using data from the Canadian Cancer Registry. *Cancer Epidemiol* 2010; 34: 550-5.
376. Herszényi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. *Eur Rev Med Pharmacol Sci* 2010; 14: 249-58.
377. Rutegård M, Shore R, Lu Y, Lagergren P, Lindblad M. Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970-2006. *Eur J Cancer* 2010; 46: 1093-100.

378. El-Rayes BF, Jasti P, Severson RK, Almhanna K, Philip PA, Shields A, Zalupski M, Heilbrun LK. Impact of race, age, and socioeconomic status on participation in pancreatic cancer clinical trials. *Pancreas* 2010; 39: 967-71.
379. Mousavi SM, Sundquist J, Hemminki K. Does immigration play a role in the risk of pancreatic cancer? A study on immigrants to Sweden. *Pancreas* 2010; 39: 1118-20 (letter).
380. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, Olsen A, Tjønneland A, Clavel-Chapelon F, Boutron-Ruault MC, Kaaks R, Rohrmann S, Boeing H, Nöthlings U, Trichopoulou A, Moutsiou E, Dillis V, Palli D, Krogh V, Panico S, Tumino R, Vineis P, van Gils CH, Peeters PH, Lund E, Gram IT, Rodríguez L, Agudo A, Larrañaga N, Sánchez MJ, Navarro C, Barricarte A, Manjer J, Lindkvist B, Sund M, Ye W, Bingham S, Khaw KT, Roddam A, Key T, Boffetta P, Duell EJ, Jenab M, Gallo V, Riboli E. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010; 126: 2394-403.
381. Ray G, Henson DE, Schwartz AM. Cigarette smoking as a cause of cancers other than lung cancer: an exploratory study using the Surveillance, Epidemiology, and End Results Program. *Chest* 2010; 138: 491-9.
382. Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. *Eur J Cancer* 2010; 46: 2581-92.
383. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, Fuchs CS, Gross MD, Jacobs EJ, Lacroix AZ, Petersen GM, Stolzenberg-Solomon RZ, Zheng W, Albanes D, Amundadottir L, Bamlet WR, Barricarte A, Bingham SA, Boeing H, Boutron-Ruault MC, Buring JE, Chanock SJ, Clipp S, Gaziano JM, Giovannucci EL, Hankinson SE, Hartge P, Hoover RN, Hunter DJ, Hutchinson A, Jacobs KB, Kraft P, Lynch SM, Manjer J, Manson JE, McTiernan A, McWilliams RR, Mendelsohn JB, Michaud DS, Palli D, Rohan TE, Slimani N, Thomas G, Tjønneland A, Tobias GS, Trichopoulos D, Virtamo J, Wolpin BM, Yu K, Zeleniuch-Jacquotte A, Patel AV; Pancreatic Cancer Cohort Consortium (PanScan). Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med* 2010; 170: 791-802.
384. McWilliams RR, Matsumoto ME, Burch PA, Kim GP, Halfdanarson TR, de Andrade M, Reid-Lombardo K, Bamlet WR. Obesity adversely affects survival in pancreatic cancer patients. *Cancer* 2010; 116: 5054-62.
385. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* 2010; 46: 2593-604.
386. O'Rourke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis. *Int J Cancer* 2010; 126: 2957-68.
387. van Boeckel PG, Boshuizen HC, Siersema PD, Vrieling A, Kunst AE, Ye W, Sund M, Michaud DS, Gallo V, Spencer EA, Trichopoulou A, Benetou V, Orfanos P, Cirera L, Duell EJ, Rohrmann S, Hemann S, Masala G, Manjer J, Mattiello A, Lindkvist B, Sánchez MJ, Pala V, Peeters PH, Braaten T, Tjønneland A, Dalton SO, Larranaga N, Dorronsoro M, Overvad K, Illner AK, Ardanaz E, Marron M, Straif K, Riboli E, Bueno-de-Mesquita B. No association between educational level and pancreatic cancer incidence in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol* 2010 Sep 7 [Epub ahead of print].
388. Kosaka T, Tajima Y, Kuroki T, Mishima T, Adachi T, Tsuneoka N, Fukuda K, Kanematsu T. *Helicobacter bilis* colonization of the biliary system in patients with pancreaticobiliary maljunction. *Br J Surg* 2010; 97: 544-9.
389. Olson SH, Chou JF, Ludwig E, O'Reilly E, Allen PJ, Jarnagin WR, Bayuga S, Simon J, Gonen M, Reisacher WR, Kurtz RC. Allergies, obesity, other risk factors and survival from pancreatic cancer. *Int J Cancer* 2010; 127: 2412-9.

390. Bradley MC, Hughes CM, Cantwell MM, Napolitano G, Murray LJ. Non-steroidal anti-inflammatory drugs and pancreatic cancer risk: a nested case-control study. *Br J Cancer* 2010; 102: 1415-21.
391. Nekolla EA, Walsh L, Spiess H. Incidence of malignant diseases in humans injected with radium-224. *Radiat Res* 2010; 174: 377-86.
392. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Ultraviolet B irradiance and vitamin D status are inversely associated with incidence rates of pancreatic cancer worldwide. *Pancreas* 2010; 39: 669-74.
393. Meinhold CL, Dodd KW, Jiao L, Flood A, Shikany JM, Genkinger JM, Hayes RB, Stolzenberg-Solomon RZ. Available carbohydrates, glycemic load, and pancreatic cancer: is there a link? *Am J Epidemiol* 2010; 171: 1174-82.
394. Wen CP, Tsai MK, Chung WS, Hsu HL, Chang YC, Chan HT, Chiang PH, Cheng TY, Tsai SP. Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. *Cancer Causes Control* 2010; 21: 1427-35.
395. Arab L. Epidemiologic evidence on coffee and cancer. *Nutr Cancer* 2010; 62: 271-83.
396. Li WQ, Kuriyama S, Li Q, Nagai M, Hozawa A, Nishino Y, Tsuji I. Citrus consumption and cancer incidence: the Ohsaki cohort study. *In J Cancer* 2010; 127: 1913-22.
397. Gong Z, Holly EA, Wang F, Chan JM, Bracci PM. Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. *Int J Cancer* 2010; 127: 1893-904.
398. Druesne-Pecollo N, Latino-Martel P, Norat T, Barrandon E, Bertrais S, Galan P, Hercberg S. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. *Int J Cancer* 2010; 127: 172-84.
399. Toner CD, Davis CD, Milner JA. The vitamin D and cancer conundrum: aiming at a moving target. *J Am Diet Assoc* 2010; 110: 1492-500.
400. Helzlsouer KJ; VDPDP Steering Committee. Overview of the cohort consortium vitamin D pooling project of rarer cancers. *Am J Epidemiol* 2010; 172: 4-9.
401. McCullough ML, Weinstein SJ, Freedman DM, Helzlsouer K, Flanders WD, Koenig K, Kolonel L, Laden F, Le Marchand L, Purdue M, Snyder K, Stevens VL, Stolzenberg-Solomon R, Virtamo J, Yang G, Yu K, Zheng W, Albanes D, Ashby J, Bertrand K, Cai H, Chen Y, Gallicchio L, Giovannucci E, Jacobs EJ, Hankinson SE, Hartge P, Hartmuller V, Harvey C, Hayes RB, Horst RL, Shu XO. Correlates of circulating 25-hydroxyvitamin D: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172: 21-35.
402. Gallicchio L, Helzlsouer KJ, Chow WH, Freedman DM, Hankinson SE, Hartge P, Hartmuller V, Harvey C, Hayes RB, Horst RL, Koenig KL, Kolonel LN, Laden F, McCullough ML, Parisi D, Purdue MP, Shu XO, Snyder K, Stolzenberg-Solomon RZ, Tworoger SS, Varanasi A, Virtamo J, Wilkens LR, Xiang YB, Yu K, Zeleniuch-Jacquotte A, Zheng W, Abnet CC, Albanes D, Bertrand K, Weinstein SJ. Circulating 25-hydroxyvitamin D and the risk of rarer cancers: design and methods of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172: 10-20.
403. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, Qi D, Patel AV, Helzlsouer KJ, Weinstein SJ, McCullough ML, Purdue MP, Shu XO, Snyder K, Virtamo J, Wilkins LR, Yu K, Zeleniuch-Jacquotte A, Zheng W, Albanes D, Cai Q, Harvey C, Hayes R, Clipp S, Horst RL, Irish L, Koenig K, Le Marchand L, Kolonel LN. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172: 81-93.
404. Bao Y, Ng K, Wolpin BM, Michaud DS, Giovannucci E, Fuchs CS. Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. *Br J Cancer* 2010; 102: 1422-7.

405. Saruc M, Iki K, Pour PM. Morphometric studies in human pancreatic cancer argues against the etiological role of type 2 diabetes in pancreatic cancer. *Histol Histopathol* 2010; 25: 423-32.
406. Douglas JB, Silverman DT, Pollak MN, Tao Y, Soliman AS, Stolzenberg-Solomon RZ. Serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 2298-306.
407. Chang CC, Chiu HF, Yang CY. Parity, age at first birth, and risk of death from pancreatic cancer: evidence from a cohort in Taiwan. *Pancreas* 2010; 39: 567-71.
408. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. *Eur J Cancer* 2010 Sep 9 [Epub ahead of print].
409. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 2010; 102: 502-5.
410. Gasull M, Porta M, Pumarega J, Vioque J, Bosch de Basea M, Puigdomènech E, Morales E, Grimalt JO, Malats N. The relative influence of diet and serum concentrations of organochlorine compounds on K-ras mutations in exocrine pancreatic cancer. *Chemosphere* 2010; 79: 686-97.
411. Chiu HF, Tsai SS, Wu TN, Yang CY. Effect modification of the association between trihalomethanes and pancreatic cancer by drinking water hardness: evidence from an ecological study. *Environ Res* 2010; 110: 513-8.
412. Klint A, Engholm G, Storm HH, Tryggvadóttir L, Gislum M, Hakulinen T, Bray F. Trends in survival of patients diagnosed with cancer of the digestive organs in the Nordic countries 1964-2003 followed up to the end of 2006. *Acta Oncol* 2010; 49: 578-607.
413. Storm HH, Engholm G, Hakulinen T, Tryggvadóttir L, Klint A, Gislum M, Kejs AM, Bray F. Department of Cancer Prevention and Documentation, Danish Cancer Society, Survival of patients diagnosed with cancer in the Nordic countries up to 1999-2003 followed to the end of 2006. A critical overview of the results. *Acta Oncol* 2010; 49: 532-44.
414. Bouvier AM, David M, Jooste V, Chauvenet M, Lepage C, Faivre J. Rising incidence of pancreatic cancer in France. *Pancreas* 2010; 1243-6.
415. Aarts MJ, van der Aa MA, Coebergh JW, Louwman WJ. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 2010; 46: 2633-46.
416. Storm HH, Gislum M, Kejs AM, Engholm G. Survival of Danish cancer patients 1995-2006. *Ugeskr Laeger* 2010; 172: 2213-7 (in Danish).
417. Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res* 2010; 16: 5028-37.
418. Sima CS, Panageas KS, Schrag D. Cancer screening among patients with advanced cancer. *JAMA* 2010; 304: 1584-91.
419. Ding Y, Cravero JD, Adrian K, Grippo P. Modeling pancreatic cancer in vivo: from xenograft and carcinogen-induced systems to genetically engineered mice. *Pancreas* 2010; 39: 283-92.
420. Dong X, Javle M, Hess KR, Shroff R, Abbruzzese JL, Li D. Insulin-like growth factor axis gene polymorphisms and clinical outcomes in pancreatic cancer. *Gastroenterology* 2010; 139: 464-73.
421. Liu Y, ElSawa SF, Almada LL. Pancreatology primers on molecular pathways – cycling toward pancreatic cancer. *Pancreatology* 2010; 10: 6-13.

422. Mohelnikova-Duchonova B, Vrana D, Holcatova I, Ryska M, Smerhovsky Z, Soucek P. CYP2A13, ADH1B, and ADH1C gene polymorphisms and pancreatic cancer. *Pancreas* 2010; 39: 144-8.
423. Mihaljevic AL, Michalski CW, Friess H, Kleeff J. Molecular mechanism of pancreatic cancer – understanding proliferation, invasion, and metastasis. *Langenbecks Arch Surg* 2010; 395: 295-308.
424. Tang H, Dong X, Day RS, Hassan MM, Li D. Antioxidant genes, diabetes and dietary antioxidants in association with risk of pancreatic cancer. *Carcinogenesis* 2010; 31: 607-13.
425. Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of b7-h1 and b7-1 expressions in pancreatic carcinoma. *World J Surg* 2010; 34: 1059-65.
426. Shao Y, Zhang W, Zhang C, Wu Q, Yang H, Zhang J, Guan M, Wan J, Yu B. High-resolution melting analysis of BLU methylation levels in gastric, colorectal, and pancreatic cancers. *Cancer Invest* 2010; 28: 642-8.
427. Theodoropoulos GE, Michalopoulos NV, Panoussopoulos SG, Taka S, Gazouli M. Effects of caspase-9 and survivin gene polymorphisms in pancreatic cancer risk and tumor characteristics. *Pancreas* 2010; 39: 976-80.
428. Han F, Zhu HG. Caveolin-1 regulating the invasion and expression of matrix metalloproteinase (MMPs) in pancreatic carcinoma cells. *J Surg Res* 2010; 159: 443-50.
429. Takano S, Sogawa K, Yoshitomi H, Shida T, Mogushi K, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Ishihara T, Tanaka H, Yokosuka O, Nomura F, Miyazaki M. Increased circulating cell signalling phosphoproteins in sera are useful for the detection of pancreatic cancer. *Br J Cancer* 2010; 103: 223-31.
430. Chapman JV, Gouazé-Andersson V, Messner MC, Flowers M, Karimi R, Kester M, Barth BM, Liu X, Liu YY, Giuliano AE, Cabot MC. Metabolism of short-chain ceramide by human cancer cells – implications for therapeutic approaches. *Biochem Pharmacol* 2010; 80: 308-15.
431. Kuuselo R, Simon R, Karhu R, Tennstedt P, Marx AH, Izbicki JR, Yekebas E, Sauter G, Kallioniemi A. 19q13 amplification is associated with high grade and stage in pancreatic cancer. *Genes Chromosomes Cancer* 2010; 49: 569-75.
432. Vizio B, Novarino A, Giacobino A, Cristiano C, Prati A, Brondino G, Ciuffreda L, Bellone G. Pilot study to relate clinical outcome in pancreatic carcinoma and angiogenic plasma factors/circulating mature/progenitor endothelial cells: preliminary results. *Cancer Sci* 2010; 101: 2448-54.
433. Sanada Y, Hirose Y, Osada S, Tanaka Y, Takahashi T, Yamaguchi K, Yoshida K. Immunohistochemical study of claudin 18 involvement in intestinal differentiation during the progression of intraductal papillary mucinous neoplasm. *Anticancer Res* 2010; 30: 2995-3003.
434. Kamio Y, Maeda K, Moriya T, Takasu N, Takeshita A, Hirai I, Kimura W, Yamakawa M. Clinicopathological significance of cell cycle regulatory factors and differentiation-related factors in pancreatic neoplasms. *Pancreas* 2010; 39: 345-52.
435. Frolov A, Liles JS, Kossenkov AV, Tzeng CW, Jhala N, Kulesza P, Varadarajulu S, Eloubeidi M, Heslin MJ, Arnoletti JP. Epidermal growth factor receptor (EGFR) intron 1 polymorphism and clinical outcome in pancreatic adenocarcinoma. *Am J Surg* 2010; 200: 398-405.
436. Mees ST, Mardin WA, Wendel C, Baeumer N, Willscher E, Senninger N, Schleicher C, Colombo-Benkmann M, Haier J. EP300 – a miRNA-regulated metastasis suppressor gene in ductal adenocarcinomas of the pancreas. *Int J Cancer* 2010; 126: 114-24.
437. Cano CE, Motoo Y, Iovanna JL. Epithelial-to-mesenchymal transition in pancreatic adenocarcinoma. *Scientific World Journal* 2010; 10: 1947-57.

438. Cui Y, Li T, Zhang D, Han J. Expression of Ezrin and phosphorylated Ezrin (pEzrin) in pancreatic ductal adenocarcinoma. *Cancer Invest* 2010; 28: 242-7.
439. Radu A, Pichon C, Camparo P, Antoine M, Allory Y, Couvelard A, Fromont G, Hai MT, Ghinea N. Expression of follicle-stimulating hormone receptor in tumor blood vessels. *N Eng J Med* 2010; 363: 1621-30.
440. Matsumoto H, Shinzaki S, Narisada M, Kawamoto S, Kuwamoto K, Moriwaki K, Kanke F, Satomura S, Kumada T, Miyoshi E. Clinical application of a lectin-antibody ELISA to measure fucosylated haptoglobin in sera of patients with pancreatic cancer. *Clin Chem Lab Med* 2010; 48: 505-12.
441. Zhang W, Li T, Shao Y, Zhang C, Wu Q, Yang H, Zhang J, Guan M, Yu B, Wan J. Semi-quantitative detection of GADD45-gamma methylation levels in gastric, colorectal and pancreatic cancers using methylation-sensitive high-resolution melting analysis. *J Cancer Res Clin Oncol* 2010; 136: 1267-73.
442. Barakat O, Rodriguez GC, Raijman I, Allison PM, Nieto J, Ozaki CF, Wood RP, Engler DA. Clinical value of plasma hepatocyte growth factor measurement for the diagnosis of periampullary cancer and prognosis after pancreaticoduodenectomy. *J Surg Oncol* 2010 Sep 1 [Epub ahead of print].
443. Rogosnitzky M, Danks R. Validation of blood testing for K-ras mutations in colorectal and pancreatic cancer. *Anticancer Res* 2010; 30: 2943-7.
444. Chen H, Tu H, Meng ZQ, Chen Z, Wang P, Liu LM. K-ras mutational status predicts poor prognosis in unresectable pancreatic cancer. *Eur J Surg Oncol* 2010; 36: 657-62.
445. Mitsunaga S, Fujii S, Ishii G, Kinoshita T, Hasebe T, Aoyagi K, Sasaki H, Ochiai A. Nerve invasion distance is dependent on laminin gamma2 in tumors of pancreatic cancer. *Int J Cancer* 2010; 127: 805-19.
446. Hanoun N, Delpu Y, Suriawinata AA, Bournet B, Bureau C, Selves J, Tsongalis GJ, Dufresne M, Buscail L, Cordelier P, Torrisani J. The silencing of microRNA 148a production by DNA hypermethylation is an early event in pancreatic carcinogenesis. *Clin Chem* 2010; 56: 1107-18.
447. Li A, Omura N, Hong SM, Vincent A, Walter K, Griffith M, Borges M, Goggins M. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. *Cancer Res* 2010; 70: 5226-37.
448. Rachagani S, Kumar S, Batra SK. MicroRNA in pancreatic cancer: pathological, diagnostic and therapeutic implications. *Cancer Lett* 2010; 292: 8-16.
449. Hanoun N, Delpu Y, Suriawinata AA, Bournet B, Bureau C, Selves J, Tsongalis GJ, Dufresne M, Buscail L, Cordelier P, Torrisani J. The silencing of microRNA 148a production by DNA hypermethylation is an early event in pancreatic carcinogenesis. *Clin Chem* 2010; 56: 1107-18.
450. Giovannetti E, Funel N, Peters GJ, Del Chiaro M, Erozcenci LA, Vasile E, Leon LG, Pollina LE, Groen A, Falcone A, Danesi R, Campani D, Verheul HM, Boggi U. MicroRNA-21 in pancreatic cancer: correlation with clinical outcome and pharmacologic aspects underlying its role in the modulation of gemcitabine activity. *Cancer Res* 2010; 70: 4528-38.
451. Corbo V, Ritelli R, Barbi S, Funel N, Campani D, Bardelli A, Scarpa A. Mutational profiling of kinases in human tumours of pancreatic origin identifies candidate cancer genes in ductal and ampulla of Vater carcinomas. *PLoS One* 2010; 5: e12653.
452. Ceyhan GO, Schäfer KH, Kerscher AG, Rauch U, Demir IE, Kadihasanoglu M, Böhm C, Müller MW, Büchler MW, Giese NA, Erkan M, Friess H. Nerve growth factor and artemin are paracrine mediators of pancreatic neuropathy in pancreatic adenocarcinoma. *Ann Surg* 2010; 251: 923-31.

453. Gold DV, Goggins M, Modrak DE, Newsome G, Liu M, Shi C, Hruban R, Goldenberg DM. Detection of early-stage pancreatic adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2010 Sep 1 [Epub ahead of print].
454. Chen JY, Amos CI, Merriman, Kelly KW, Wei QY, Sen S, Killary AM, Frazier ML. Genetic variants of p21 and p27 and pancreatic cancer risk in non-Hispanic whites: a case-control study. *Pancreas* 2010; 39: 1-4.
455. Wang F, Larsson J, Herrington MK, Permert J. PP56 improves energy homeostasis in a mouse model of pancreatic cancer. *Tumour Biol* 2010; 31: 309-13.
456. Xu X, Ehdai B, Ohara N, Yoshino T, Deng CX. Synergistic action of Smad4 and Pten in suppressing pancreatic ductal adenocarcinoma formation in mice. *Oncogene* 2010; 29: 674-86.
457. Hrabar D, Aralica G, Gomercic M, Ljubic N, Kruslin B, Tomas D. Epithelial and stromal expression of syndecan-2 in pancreatic carcinoma. *Anticancer Res* 2010; 30: 2749-53.
458. Kim JH, Choi YD, Lee JS, Lee JH, Nam JH, Choi C. Utility of thyroid transcription factor-1 and CDX-2 in determining the primary site of metastatic adenocarcinomas in serous effusions. *Acta Cytol* 2010; 54: 277-82.
459. Naccarati A, Pardini B, Polakova V, Smerhovsky Z, Vodickova L, Soucek P, Vrana D, Holcatova I, Ryska M, Vodicka P. Genotype and haplotype analysis of TP53 gene and the risk of pancreatic cancer: an association study in the Czech Republic. *Carcinogenesis* 2010; 31: 666-70.
460. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Iacobuzio-Donahue CA. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; 467: 1114-7.
461. Campbell PJ, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, Morsberger LA, Latimer C, McLaren S, Lin ML, McBride DJ, Varela I, Nik-Zainal SA, Leroy C, Jia M, Menzies A, Butler AP, Teague JW, Griffin CA, Burton J, Swerdlow H, Quail MA, Stratton MR, Iacobuzio-Donahue C, Futreal PA. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature* 2010; 467:1109-13.
462. Cano CE, Iovanna JL. Stress proteins and pancreatic cancer metastasis. *Sci World J* 2010; 10: 1958-66.
463. Sabbaghian MS, Rothberger G, Alongi AP, Gagner JP, Goldberg JD, Rolnitzky L, Chiriboga L, Hajdu CH, Zagzag D, Basch R, Shamamian P. Levels of elevated circulating endothelial cell decline after tumor resection in patients with pancreatic ductal adenocarcinoma. *Anticancer Res* 2010; 30: 2911-7.
464. Aloysius MM, Hewavisenthi SJ, Bates TE, Rowlands BJ, Lobo DN, Zaitoun AM. Predictive value of tumor proliferative indices in periampullary cancers: Ki-67, mitotic activity index (MI) and volume corrected mitotic index (M/V) using tissue microarrays. *World J Surg* 2010; 34: 2115-21.
465. Aloysius MM, Zaitoun AM, Awad S, Ilyas M, Rowlands BJ, Lobo DN. Mucins and CD56 as markers of tumour invasion and prognosis in periampullary cancer. *Br J Surg* 2010; 97: 1269-78.
466. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. *Am J Surg* 2010; 200: 197-203.
467. Liang JJ, Zhu S, Bruggeman R, Zaino RJ, Evans DB, Fleming JB, Gomez HF, Zander DS, Wang H. High levels of expression of human stromal cell-derived factor-1 are associated with worse prognosis in patients with stage II pancreatic ductal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2010 sep 14 [Epub ahead of print].
468. Jørgensen MT, Heegaard NHH, Schaffalitzky de Muckadell OB. Comparison of plasma Tu-M2-PK and CA19-9 in pancreatic cancer. *Pancreas* 2010; 39: 243-7.

469. Guo Q, Kang M, Zhang B, Chen Y, Dong X, Wu Y. Elevated levels of CA 19-9 and CEA in pancreatic cancer-associated diabetes. *J Cancer Res Clin Oncol* 2010; 136: 1627-31.
470. Motoi F, Rikiyama T, Katayose Y, Egawa SI, Unno M. Retrospective evaluation of the influence of postoperative tumor marker status on survival and patterns of recurrence after surgery for pancreatic cancer based on RECIST guidelines. *Ann Surg Oncol* 2010 Sep 15 [Epub ahead of print].
471. Kondo N, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Nakashima A, Sakabe R, Shigemoto N, Kato Y, Ohge H, Sueda T. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. *Ann Surg Oncol* 2010; 17: 2321-9.
472. Chen R, Crispin DA, Pan S, Hawley S, McIntosh MW, May D, Anton-Culver H, Ziogas A, Bronner MP, Brentnall TA. Pilot study of blood biomarker candidates for detection of pancreatic cancer. *Pancreas* 2010; 39: 981-8.
473. Gowda GA. Human bile as a rich source of biomarkers for hepatopancreatobiliary cancers. *Biomark Med* 2010; 4: 299-314.
474. Karamitopoulou E, Zlobec I, Tornillo L, Carafa V, Schaffner T, Brunner T, Borner M, Diamantis I, Zimmermann A, Terracciano L. Differential cell cycle and proliferation marker expression in ductal pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia (PanIN). *Pathology* 2010; 42: 229-34.
475. Hong X, Michalski CW, Kong B, Zhang W, Raggi MC, Sauliunaite D, De Oliveira T, Friess H, Kleeff J. ALCAM is associated with chemoresistance and tumor cell adhesion in pancreatic cancer. *J Surg Oncol* 2010; 101: 564-9.
476. Chen R, Crispin DA, Pan S, Hawley S, McIntosh MW, [S]; May D, Anton-Culver H, Ziogas A, Bronner MP, Brentnall TA. Pilot study of blood biomarker candidates for detection of pancreatic cancer. *Cancer* 2010; 39: 981-8.
477. Fisher JM, Gordon SR, Gardner TB. The impact of prior biliary stenting on the accuracy and complication rate of endoscopic ultrasound fine-needle aspiration for diagnosing pancreatic adenocarcinoma. *Pancreas* 2011; 40: 16-20.
478. Parsi MA, Deepinder F, Lopez R, Stevens T, Dodig M, Zuccaro G. Factors affecting the yield of brush cytology for the diagnosis of pancreatic and biliary cancers. *Pancreas* 2011; 40: 46-51.
479. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; 139: 1172-80.
480. Tannapfel A, Wittekind C. The current TNM system for gastrointestinal tumors part II. *Pathologe* 2010; 31: 348-52 (in German).
481. Kopantzev EP, Vayshlya NA, Kopantseva MR, Egorov VI, Pikunov M, Zinovyeva MV, Vinogradova TV, Zborovskaya IB, Sverdlov ED. Cellular and molecular phenotypes of proliferating stromal cells from human carcinomas. *Br J Cancer* 2010; 102: 1533-40.
482. Liszka Ł, Pajak J, Zielińska-Pajak E, Gołka D, Mrowiec S, Lampe P. Different approaches to assessment of lymph nodes and surgical margin status in patients with ductal adenocarcinoma of the pancreas treated with pancreaticoduodenectomy. *Pathology* 2010; 42: 138-46.
483. Masugi Y, Yamazaki K, Hibi T, Aiura K, Kitagawa Y, Sakamoto M. Solitary cell infiltration is a novel indicator of poor prognosis and epithelial-mesenchymal transition in pancreatic cancer. *Hum Pathol* 2010; 41: 1061-8.
484. Kayahara M, Funaki K, Tajima H, Takamura H, Ninomiya I, Kitagawa H, Ohta T. Surgical implication of micrometastasis for pancreatic cancer. *Pancreas* 2010; 39: 884-8.

485. Kurahara H, Takao S, Shinchi H, Maemura K, Mataka Y, Sakoda M, Hayashi T, Kuwahata T, Minami K, Ueno S, Natsugoe S. Significance of lymphangiogenesis in primary tumor and draining lymph nodes during lymphatic metastasis of pancreatic head cancer. *J Surg Oncol* 2010; 102: 809-15.
486. Prenzel KL, Hölscher AH, Vallböhmer D, Drebber U, Gutschow CA, Mönig SP, Stippel DL. Lymph node size and metastatic infiltration in adenocarcinoma of the pancreatic head. *Eur J Surg Oncol* 2010; 36: 993-6.
487. Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? *Ann Surg Oncol* 2010; 17: 2312-20.
488. Gil Z, Cavel O, Kelly K, Brader P, Rein A, Gao SP, Carlson DL, Shah JP, Fong Y, Wong RJ. Paracrine regulation of pancreatic cancer cell invasion by peripheral nerves. *J Natl Cancer Inst* 2010; 102: 107-18.
489. Matsukuma S, Sato K. Pancreatic neuroma-like lesions after upper abdominal surgery: a clinicopathological postmortem study. *Virchows Arch* 2010; 457: 651-7.
490. Layfield LJ, Jarboe EA. Cytopathology of the pancreas: neoplastic and nonneoplastic entities. *Ann Diagn Pathol* 2010; 14: 140-51.
491. Dursun N, Feng J, Basturk O, Bandyopadhyay S, Cheng JD, Adsay VN. Vacuolated cell pattern of pancreatobiliary adenocarcinoma: a clinicopathological analysis of 24 cases of a poorly recognized distinctive morphologic variant important in the differential diagnosis. *Virchows Arch* 2010; 457: 643-9.
492. Yoon SE, Byun JH, Kim KA, Kim HJ, Lee SS, Jang SJ, Jang YJ, Lee MG. Pancreatic ductal adenocarcinoma with intratumoral cystic lesions on MRI: correlation with histopathological findings. *Br J Radiol* 2010; 83: 318-26.
493. Hiraoka N, Ino Y, Sekine S, Tsuda H, Shimada K, Kosuge T, Zavada J, Yoshida M, Yamada K, Koyama T, Kanai Y. Tumour necrosis is a postoperative prognostic marker for pancreatic cancer patients with a high interobserver reproducibility in histological evaluation. *Br J Cancer* 2010; 103: 1057-65.
494. Demeure MJ, Sielaff T, Koep L, Prinz R, Moser AJ, Zeh H, Hostetter G, Black J, Decker A, Rosewell S, Bussey KJ, Von Hoff D. Multi-institutional tumor banking: lessons learned from a pancreatic cancer biospecimen repository. *Pancreas* 2010; 39: 949-54.
495. Fukuba N, Fujita K, Nakayama S, Takenaka M, Matsui S, Ozaka M, Shibagaki K, Yoshinaga H, Masuzawa A, Watanabe A, Fujiwara H, Sugahara A, Fujita T, Mukai H, Tsukamoto T, Teramura K. A case of small pancreatic cancer with intraductal progress. *Nippon Shokakibyō Gakkai Zasshi* 2010; 107: 792-7 (in Japanese).
496. Strobel O, Rosow DE, Rakhlin EY, Lauwers GY, Trainor AG, Alsina J, Fernández-Del Castillo C, Warshaw AL, Thayer SP. Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. *Gastroenterology* 2010; 138: 1166-77.
497. Recavarren C, Labow DM, Liang J, Zhang L, Wong M, Zhu H, Wang J, Francis F, Xu R. Histologic characteristics of pancreatic intraepithelial neoplasia associated with different pancreatic lesions. *Hum Pathol* 2011; 42: 18-24.
498. Rougemont AL, Genevay M, McKee TA, Gremaud M, Mentha G, Rubbia-Brandt L. Extensive biliary intraepithelial neoplasia (BillIN) and multifocal early intrahepatic cholangiocarcinoma in non-biliary cirrhosis. *Virchows Arch* 2010; 456: 711-7.
499. Lisovsky M, Dresser K, Woda B, Mino-Kenudson M. Immunohistochemistry for cell polarity protein lethal giant larvae 2 differentiates pancreatic intraepithelial neoplasia-3 and ductal adenocarcinoma of the pancreas from lower-grade pancreatic intraepithelial neoplasias. *Hum Pathol* 2010; 41: 902-9.

500. Zhang L, Farrell JJ, Zhou H, Elashoff D, Akin D, Park NH, Chia D, Wong DT. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010; 138: 949-57.
501. Nicolucci A. Epidemiological aspects of neoplasms in diabetes. *Acta Diabetol* 2010; 47: 87-95.
502. Bartosch-Härlid A, Andersson R. Diabetes mellitus in pancreatic cancer and the need for diagnosis of asymptomatic disease. *Pancreatol* 2010; 10: 423-8.
503. Dong X, Tang H, Hess KR, Abbruzzese JL, Li D. Glucose metabolism gene polymorphisms and clinical outcome in pancreatic cancer. *Cancer* 2010 Sep 15 [Epub ahead of print].
504. Johansen D, Stocks T, Jonsson H, Lindkvist B, Björge T, Concin H, Almquist M, Häggström C, Engeland A, Ulmer H, Hallmans G, Selmer R, Nagel G, Tretli S, Stattin P, Manjer J. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 2307-17.
505. Call R, Grimsley M, Cadwallader L, Cialone L, Hill M, Hreish V, King ST, Riche DM. Insulin – carcinogen or mitogen? Preclinical and clinical evidence from prostate, breast, pancreatic, and colorectal cancer research. *Postgrad Med* 2010; 122: 158-65.
506. Rensing KL, Houttuijn Bloemendaal FM, Weijers EM, Richel DJ, Büller HR, Koolwijk P, van der Loos CM, Twickler TB, von der Thüsen JH. Could recombinant insulin compounds contribute to adenocarcinoma progression by stimulating local angiogenesis? *Diabetologica* 2010; 53: 966-70.
507. Tsugane S, Inoue M. Insulin resistance and cancer: epidemiological evidence. *Cancer Sci* 2010; 101: 1073-9.
508. Sugiyama Y, Tanno S, Nishikawa T, Nakamura K, Sasajima J, Koizumi K, Mizukami Y, Karasaki H, Kasai S, Yoshida Y, Watanabe N, Okumura T, Kohgo Y. A case of pancreatic carcinoma presenting as pancreaticopleural fistula with pancreatic pleural effusion. *Nippon Shokakibyo Gakkai Zasshi* 2010; 107: 784-91 (in Japanese).
509. Demir IE, Ceyhan GO, Rauch U, Altintas B, Klotz M, Müller MW, Büchler MW, Friess H, Schäfer KH. The microenvironment in chronic pancreatitis and pancreatic cancer induces neuronal plasticity. *Neurogastroenterol Motil* 2010; 22: 480-90.
510. Yang DM, Kim HC, Ryu JK, Joo KR, Ahn KJ. Sonographic appearance of focal fatty infiltration of the pancreas. *J Clin Ultrasound* 2010; 38: 45-7.
511. Galasso D, Carnuccio A, Larghi A. Pancreatic cancer: diagnosis and endoscopic staging. *Eur Rev Med Pharmacol Sci* 2010; 14: 375-85.
512. Ainsworth AP, Hansen T, Frstrup CW, Mortensen MB. Indications for and clinical impact of repeat endoscopic ultrasound. *Scand J Gastroenterol* 2010; 45: 477-82.
513. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. *Abdom Imaging* 2010; 35: 163-71.
514. Grieser C, Steffen IG, Grajewski L, Stelter L, Streitparth F, Schnapauff D, Glanemann M, Langrehr J, Andreou A, Neuhaus P, Hamm B, Hänninen EL, Denecke T. Preoperative multidetector row computed tomography for evaluation and assessment of resection criteria in patients with pancreatic masses. *Acta Radiol* 2010; 51: 1067-77.
515. Kim JH, Park SH, Yu ES, Kim MH, Kim J, Byun JH, Lee SS, Hwang HJ, Hwang JY, Lee SS, Lee MG. Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. *Radiology* 2010; 257: 87-96.

516. Hattori Y, Gabata T, Zen Y, Mochizuki K, Kitagawa H, Matsui O. Poorly enhanced areas of pancreatic adenocarcinomas on late-phase dynamic computed tomography: comparison with pathological findings. *Pancreas* 2010; 39: 1263-70.
517. Sai M, Mori H, Kiyonaga M, Kosen K, Yamada Y, Matsumoto S. Peripancreatic lymphatic invasion by pancreatic carcinoma: evaluation with multi-detector row CT. *Abdom Imaging* 2010; 35: 154-62.
518. Hata H, Mori H, Matsumoto S, Yamada Y, Kiyosue H, Tanoue S, Hongo N, Kashima K. Fibrous stroma and vascularity of pancreatic carcinoma: correlation with enhancement patterns on CT. *Abdom Imaging* 2010; 35: 172-80.
519. Marin D, Nelson RC, Schindera ST, Richard S, Youngblood RS, Yoshizumi TT, Samei E. Low-tube-voltage, high-tube-current multidetector abdominal CT: improved image quality and decreased radiation dose with adaptive statistical iterative reconstruction algorithm--initial clinical experience. *Radiology* 2010; 254: 145-53.
520. Macari M, Spieler B, Kim D, Graser A, Megibow AJ, Babb J, Chandarana H. Dual-source dual-energy MDCT of pancreatic adenocarcinoma: initial observations with data generated at 80 kVp and at simulated weighted-average 120 kVp. *Am J Roentgenol* 2010; 194: W27-32.
521. Fusari M, Maurea S, Imbriaco M, Mollica C, Avitabile G, Soscia F, Camera L, Salvatore M. Comparison between multislice CT and MR imaging in the diagnostic evaluation of patients with pancreatic masses. *Radiol Med* 2010; 115: 453-66.
522. Tajima Y, Kuroki T, Tsuneoka N, Adachi T, Isomoto I, Uetani M, Kanematsu T. Monitoring fibrosis of the pancreatic remnant after a pancreaticoduodenectomy with dynamic MRI. *J Surg Res* 2010; 158: 61-8.
523. Lauenstein T, Martin DR, Sarmiento JM, Kalb B, Moreira R, Carew J, Salman K, Adsay V. Pancreatic adenocarcinoma tumor grade determination using contrast-enhanced magnetic resonance imaging. *Pancreas* 2010; 39: 71-5.
524. Koizumi M, Sata N, Kasahara N, Morishima K, Sasanuma H, Sakuma Y, Shimizu A, Hyodo M, Yasuda Y. Remnant pancreatectomy for recurrent or metachronous pancreatic carcinoma detected by FDG-PET: two case reports. *JOP* 2010; 11: 36-40.
525. Harris MD, Buscaglia JM. How to do pancreatic mass FNA. *Gastrointest Endosc* 2010; 71: 825-6.
526. Rodriguez S, Faigel D. Absence of a dilated duct predicts benign disease in suspected pancreas cancer: a simple clinical rule. *Dig Dis Sci* 2010; 55: 1161-6.
527. Will U, Mueller A, Topalidis T, Meyer F. Value of endoscopic ultrasonography-guided fine needle aspiration (FNA) in the diagnosis of neoplastic tumor(-like) pancreatic lesions in daily clinical practice. *Ultraschall Med* 2010; 31: 169-74.
528. Levy MJ, Gleeson FC, Campion MB, Caudill JL, Clain JE, Halling K, Rajan E, Topazian MD, Wang KK, Wiersema MJ, Clayton A. Prospective cytological assessment of gastrointestinal luminal fluid acquired during EUS: a potential source of false-positive FNA and needle tract seeding. *Am J Gastroenterol* 2010; 105: 1311-8.
529. Manzia TM, Toti L, Lenci I, Attia M, Tariciotti L, Bramhall SR, Buckels JA, Mirza DF. Benign disease and unexpected histological findings after pancreaticoduodenectomy: the role of endoscopic ultrasound fine needle aspiration. *Ann R Coll Surg Eng* 2010; 92: 295-301.
530. Atwell TD, Smith RL, Hesley GK, Callstrom MR, Schleck CD, Harmsen WS, Charboneau JW, Welch TJ. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *AJR Am Roentgenol* 2010; 194: 784-9.

531. Toll AD, Bibbo M. Identification of gastrointestinal contamination in endoscopic ultrasound-guided pancreatic fine needle aspiration. *Acta Cytol* 2010; 54: 245-8.
532. Alsharif M, Carlo-Demovich J, Massey C, Madory JE, Lewin D, Medina AM, Recavarren R, Houser PM, Yang J. Telecytopathology for immediate evaluation of fine-needle aspiration specimens. *Cancer Cytopathol* 2010; 118: 119-26.
533. Khashab MAM, Emerson RE, DeWitt J. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of anaplastic pancreatic carcinoma: a single-center experience. *Pancreas* 2010; 39: 88-91.
534. Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. *Surgeon* 2010; 8: 239-46.
535. Lin J, Jing X. Fine-needle aspiration of intrapancreatic accessory spleen, mimic of pancreatic neoplasms. *Arch Pathol Lab Med* 2010; 134: 1474-8.
536. Ziegler KM, Pitt HA, Zyromski NJ, Chauhan A, Sherman S, Moffatt D, Lehman GA, Lillemoe KD, Rescorla FJ, West KW, Grosfeld JL. Choledochoceles: are they choledochal cysts? *Ann Surg* 2010; 252: 683-90.
537. Konstantinidis IT, Warshaw AL, Deshpande V, Sahani D, Berger D, Fernandez-del Castillo C, Ferrone CR. Cholesterol crystal embolization presenting as either solid or cystic pancreatic lesion. *J Surg Oncol* 2010; 102: 706-8.
538. Oliveira-Cunha M, Byers RJ, Siriwardena A. Poly(adenylic acid) complementary DNA real-time polymerase chain reaction in pancreatic ductal juice in patients undergoing pancreaticoduodenectomy. *Pancreas* 2010; 39: 171-4.
539. Han L, Pansare V, Al-Abbadi M, Husain M, Feng J. Combination of MUC5ac and WT-1 immunohistochemistry is useful in distinguishing pancreatic ductal carcinoma from ovarian serous carcinoma in effusion cytology. *Diagn Cytopathol* 2010; 38: 333-6.
540. Mudan S, Giakoustidis A, Thillainayagam AV, Jacob J, Stebbing J. Clinical utility of circulating tumor cell measurement in the diagnosis of indeterminate lesions of the pancreas. *Future Oncol* 2010; 6: 177-9.
541. Liggett T, Melnikov A, Yi QL, Replogle C, Brand R, Kaul K, Talamonti M, Abrams RA, Levenson V. Differential methylation of cell-free circulating DNA among patients with pancreatic cancer versus chronic pancreatitis. *Cancer* 2010; 116: 1674-80.
542. Regino CA, Ogawa M, Alford R, Wong KJ, Kosaka N, Williams M, Feild BJ, Takahashi M, Choyke PL, Kobayashi H. Two-step synthesis of galactosylated human serum albumin as a targeted optical imaging agent for peritoneal carcinomatosis. *J Med Chem* 2010; 53: 1579-86.
543. Dumitrascu DL, Suci O, Grad C, Gheban D. Thrombotic complications of pancreatic cancer: classical knowledge revisited. *Dig Dis* 2010; 28: 350-4.
544. Poruk KE, Firpo MA, Huerter LM, Scaife CL, Emerson LL, Boucher KM, Jones KA, Mulvihill SJ. Serum platelet factor 4 is an independent predictor of survival and venous thromboembolism in patients with pancreatic adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2010 Sep 14 [Epub ahead of print].
545. Shaib W, Deng Y, Zilberman D, Lundberg B, Saif MW. Assessing risk and mortality of venous thromboembolism in pancreatic cancer patients. *Anticancer Res* 2010; 30: 4261-4.
546. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, Baron JA, Sørensen HT. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer* 2010; 103: 947-53.

547. Menapace LA, Khorana AA. The role of thromboprophylaxis in cancer patients: emerging data. *Curr Opin Hematol* 2010; 17: 450-6.
548. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, Baron JA, Sørensen HT. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer* 2010 Sep 14 [Epub ahead of print].
549. Seeger M, Günther R, Hinrichsen H, Both M, Helwig U, Arlt A, Stelck B, Bräsen JH, Sipos B, Schafmayer C, Braun F, Bröring DC, Schreiber S, Hampe J. Chronic portal vein thrombosis: transcapsular hepatic collateral vessels and communicating ectopic varices. *Radiology* 2010; 257: 568-78.
550. Locher JL, Robinson CO, Bailey FA, Carroll WR, Heimburger DC, Saif MW, Tajeu G, Ritchie CS. Disruptions in the organization of meal preparation and consumption among older cancer patients and their family caregivers. *Psychooncology* 2010; 19: 967-74.
551. Nienhuijs SW, Rutten HJ, Luiten EJ, van Driel OJ, Reemst PH, Lemmens VE, de Hingh IH. Reduction of in-hospital mortality following regionalisation of pancreatic surgery in the south-east of the Netherlands. *Eur J Surg Oncol* 2010; 36: 652-6.
552. Friese CR, Earle CC, Silber JH, Aiken LH. Hospital characteristics, clinical severity, and outcomes for surgical oncology patients. *Surgery* 2010; 147: 602-9.
553. Bilimoria KY, Bentrem DJ, Talamonti MS, Stewart AK, Winchester DP, Ko CY. Risk-based selective referral for cancer surgery: a potential strategy to improve perioperative outcomes. *Ann Surg* 2010; 251: 708-16.
554. Peros G, Giannopoulos GA, Christodoulou S, Konstantoudakis G, Petropoulou K, Sakorafas GH. Good results after major pancreatic resections in a middle-volume center. *Pancreas* 2010; 39: 411-4.
555. Sandroussi C, Brace C, Kennedy ED, Baxter NN, Gallinger S, Wei AC. Sociodemographics and comorbidities influence decisions to undergo pancreatic resection for neoplastic lesions. *J Gastrointest Surg* 2010; 14: 1401-8.
556. El-Rayes BF, Jasti P, Severson RK, Almhanna K, Philip PA, Shields A, Zalupski M, Heilbrun LK. Impact of race, age, and socioeconomic status on participation in pancreatic cancer clinical trials. *Pancreas* 2010; 39: 967-71.
557. Croome KP, Jayaraman S, Schlachta CM. Preoperative staging of cancer of the pancreatic head: is there room for improvement? *Can J Surg* 2010; 53: 171-4.
558. Weber A, Kehl V, Mittermeyer T, Herberich E, Rothling N, Schmid RM, Prinz C. Prognostic factors for survival in patients with unresectable pancreatic cancer. *Pancreas* 2010; 39: 1247-53.
559. Kuhn Y, Koscielny A, Glowka T, Hirner A, Kalff JC, Standop J. Postresection survival outcomes of pancreatic cancer according to demographic factors and socio-economic status. *Eur J Surg Oncol* 2010; 36: 496-500.
560. Bhatti I, Peacock O, Awan AK, Semeraro D, Larvin M, Hall RI. Lymph node ratio versus number of affected lymph nodes as predictors of survival for resected pancreatic adenocarcinoma. *World J Surg* 2010; 34: 768-75.
561. Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ, Imrie CW, McKay CJ, Carter R. Positive mobilization margins alone do not influence survival following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *Ann Surg* 2010; 251: 1003-10.
562. Gaedcke J, Gunawan B, Grade M, Szöke R, Liersch T, Becker H, Ghadimi BM. The mesopancreas is the primary site for R1 resection in pancreatic head cancer: relevance for clinical trials. *Langenbecks Arch Surg* 2010; 395: 451-8.

563. Belyaev O, Herden H, Meier JJ, Muller CA, Seelig MH, Herzog T, Tannapfel A, Schmidt WE, Uhl W. Assessment of pancreatic hardness—surgeon versus durometer. *J Surg Res* 2010; 158: 53-60.
564. Clark CJ, Traverso LW. Positive peritoneal lavage cytology is a predictor of worse survival in locally advanced pancreatic cancer. *Am J Surg* 2010; 199: 657-62.
565. Lavu H, Kennedy EP, Mazo R, Stewart RJ, Greenleaf C, Grenda DR, Sauter PK, Leiby BE, Croker SP, Yeo CJ. Preoperative mechanical bowel preparation does not offer a benefit for patients who undergo pancreaticoduodenectomy. *Surgery* 2010; 148: 278-84.
566. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijn JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Eng J Med* 2010; 362: 129-37.
567. Garcea G, Chee W, Ong SL, Maddern G. Preoperative biliary drainage for distal obstruction: the case against revisited. *Pancreas* 2010; 39: 119-26.
568. Eshuis WJ, van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, Kuipers EJ, Coene PP, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijn JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. *Ann Surg* 2010; 252: 840-9.
569. Augenstein VA, Reuter NP, Bower MR, McMasters KM, Scoggins CR, Martin RC. Bile cultures: a guide to infectious complications after pancreaticoduodenectomy. *J Surg Oncol* 2010; 102: 478-81.
570. Hariharan D, Constantinides VA, Froeling FE, Tekkis PP, Kocher HM. The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers – a meta-analysis. *Eur J Surg Oncol* 2010; 36: 941-8.
571. Standop J, Glowka T, Schmitz V, Schaefer N, Hirner A, Kalff J. Emergency Kausch-Whipple procedure: indications and experiences. *Pancreas* 2010; 39: 156-9.
572. Shukla PJ, Barreto SG, Fingerhut A, Bassi C, Büchler MW, Dervenis C, Gouma D, Izbicki JR, Neoptolemos J, Padbury R, Sarr MG, Traverso W, Yeo CJ, Wente MN. Toward improving uniformity and standardization in the reporting of pancreatic anastomoses: a new classification system by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2010; 147: 144-53.
573. Hashimoto Y, Traverso LW. Pancreatic anastomotic failure rate after pancreaticoduodenectomy decreases with microsurgery. *J Am Coll Surg* 2010; 211: 510-21.
574. Buc E, Flamein R, Golffier C, Dubois A, Nagarajan G, Futier E, Pezet D. Peng's binding pancreaticojejunostomy after pancreaticoduodenectomy: a French prospective study. *J Gastrointest Surg* 2010; 14: 705-10.
575. Jeyarajah DR, Khithani A, Curtis D, Galanopoulos CA. The 'Whip-Stow' procedure: an innovative modification to the Whipple procedure in the management of premalignant and malignant pancreatic head disease. *Am Surg* 2010; 76: 70-2.
576. Grobmyer SR, Kooby D, Blumgart LH, Hochwald SN. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. *J Am Coll Surg* 2010; 210: 54-9.
577. Sato S, Toyokawa H, Yanagimoto H, Yamamoto T, Hirooka S, Yui R, Yamaki, Matsui Y, Mergental H, Kwon AH. Reinforcement of pancreaticojejunostomy using polyglycolic acid mesh and fibrin glue sealant. *Pancreas* 2010; 40: 10-5.
578. Shukla PJ, Barreto SG, Fingerhut A. Do transanastomotic pancreatic ductal stents after pancreatic resections improve outcomes? *Pancreas* 2010; 39: 561-6.

579. Satoi S, Toyokawa H, Yanagimoto H, Yamamoto T, Hirooka S, Yui R, Yamaki S, Takahashi K, Matsui Y, Mergental H, Kwon A. Is a nonstented duct-to-mucosa anastomosis using the modified Kakita method a safe procedure? *Pancreas* 2010; 39: 165-70.
580. Kuroki T, Tajima Y, Kitasato A, Adach T, Kanematsu T. Stenting versus non-stenting in pancreaticojejunostomy. A prospective study limited to a normal pancreas without fibrosis sorted by using dynamic MRI. *Pancreas* 2011; 40: 21-4.
581. Alvarado-Bachmann R, Choi J, Gananadha S, Hugh TJ, Samra JS. The infracolic approach to pancreatoduodenectomy for large pancreatic head tumours invading the colon. *Eur J Surg Oncol* 2010 Sep 13 [Epub ahead of print].
582. Lee SE, Jang JY, Hwang DW, Lee KU, Kim SW. Clinical efficacy of organ-preserving pancreatectomy for benign or low-grade malignant potential lesion. *J Korean Med Sci* 2010; 25: 97-103.
583. LaFemina J, Vagefi PA, Warshaw AL, Fernández-del Castillo C. Transgastric pancreaticogastric anastomosis: an alternative operative approach for middle pancreatectomy. *Arch Surg* 2010; 145: 476-81.
584. Sudo T, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Ohge H, Sueda T. Middle pancreatectomy with pancreaticogastrostomy: a technique, operative outcomes, and long-term pancreatic function. *J Surg Oncol* 2010; 101: 61-5.
585. Shikano T, Nakao A, Kodera Y, Yamada S, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Takeda S. Middle pancreatectomy: safety and long-term results. *Surgery* 2010; 147: 21-9.
586. Alsaif F. Pylorus preserving pancreaticoduodenectomy for peri-ampullary carcinoma, is it a good option? *Saudi J Gastroenterol* 2010; 16: 75-8.
587. Hirota M, Kanemitsu K, Takamori H, Chikamoto A, Tanaka H, Sugita H, Sand J, Nordback I, Baba H. Pancreatoduodenectomy using a no-touch isolation technique. *Am J Surg* 2010; 199: e65-8.
588. Bachellier P, Rosso E, Lucescu I, Oussoultzoglou E, Tracey J, Pessaux P, Ferreira N, Jaeck D. Is the need for an arterial resection a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma? A case-matched controlled study. *J Surg Oncol* 2011; 103: 75-84.
589. Donahue TR, Reber HA. Operative blood loss and survival in pancreatic cancer. *Pancreas* 2011; 40: 1-2 (editorial).
590. Nagai S, Fujii T; Kodera Y, Kanda M, Sahin TT, Kanzaki A, Yamada S, Sugimoto H, Nomoto S, Takeda S, Morita S, Nakao A. Impact of operative blood loss on survival in invasive ductal adenocarcinoma of the pancreas. *Pancreas* 2011; 30: 3-9.
591. de Jong MC, Tsai S, Cameron JL, Wolfgang CL, Hirose K, van Vledder MG, Eckhauser F, Herman JM, Edil BH, Choti MA, Schulick RD, Pawlik TM. Safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. *J Surg Oncol* 2010; 102: 256-63.
592. Hemming AW, Magliocca JF, Fujita S, Kayler LK, Hochwald S, Zendejas I, Kim RD. Combined resection of the liver and pancreas for malignancy. *J Am Coll Surg* 2010; 210: 808-14.
593. De Jong MC, Farnell MB, Scwabas G, Cunningham SC, Cameron JL, Geschwind JF, Wolfgang CL, Herman JM, Edil BH, Choti MA, Schulick RD, Nagorney DM, Pawlik TM. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: a dual-center analysis. *Ann Surg* 2010; 252: 142-8.
594. Singh A, Singh T, Chaudhary A. Synchronous resection of solitary liver metastases with pancreaticoduodenectomy. *JOP* 2010; 11: 434-8.
595. Kendrick ML, Cusati D. Total laparoscopic pancreaticoduodenectomy: feasibility and outcome in an early experience. *Arch Surg* 2010; 145: 19-23.

596. 812. Waters JA, Canal DF, Wiebke EA, Dumas RP, Beane JD, Aguilar-Saavedra JR, Ball CG, House MG, Zyromski NJ, Nakeeb A, Pitt HA, Lillemoe KD, Schmidt CM. Robotic distal pancreatectomy: cost effective? *Surgery* 2010; 148: 814-23.
597. Narula VK, Mikami DJ, Melvin WS. Robotic and laparoscopic pancreaticoduodenectomy: a hybrid approach. *Pancreas* 2010; 39: 160-4.
598. Kang CM, Kim DH, Lee WJ, Chi HS. Initial experiences using robot-assisted central pancreatectomy with pancreaticogastrostomy: a potential way to advanced laparoscopic pancreatectomy. *Surg Endosc* 2010 Sep 11 [Epub ahead of print].
599. Horiguchi A, Uyama I, Miyakawa S. Robot-assisted laparoscopic pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci* 2010 Sep 2 [Epub ahead of print].
600. Marquez S, Marquez TT, Ikramuddin S, Kandaswamy R, Antanavicius G, Freeman ML, Hering BJ, Sutherland DER. Laparoscopic and da Vinci robot-assisted total pancreaticoduodenectomy and intraportal islet autotransplantation. Case report of a definitive minimally invasive treatment of chronic pancreatitis *Pancreas* 2010; 39: 1109-11 (letter).
601. Sugimoto M, Yasuda H, Koda K, Suzuki M, Yamazaki M, Tezuka T, Kosugi C, Higuchi R, Watayo Y, Yagawa Y, Uemura S, Tsuchiya H, Azuma T. Image overlay navigation by markerless surface registration in gastrointestinal, hepatobiliary and pancreatic surgery. *J Hepatobiliary Pancreat Sci* 2010; 17: 629-36.
602. Rieder E, Swanstrom LL. Advances in cancer surgery: Natural orifice surgery (NOTES) for oncological diseases. *Surg Oncol* 2010 Sep 8 [Epub ahead of print].
603. Christians KK, Lal A, Pappas S, Quebbeman E, Evans DB. Portal vein resection. *Surg Clin North Am* 2010; 90: 309-22.
604. Chua TC, Saxena A. Extended pancreaticoduodenectomy with vascular resection for pancreatic cancer: a systematic review. *J Gastrointest Surg* 2010; 14: 1442-52.
605. Chu CK, Farnell MB, Nguyen JH, Stauffer JA, Kooby DA, Scwab GM, Sarmiento JM. Prosthetic graft reconstruction after portal vein resection in pancreaticoduodenectomy: a multicenter analysis. *J Am Coll Surg* 2010; 211: 316-24.
606. KVN Menon, M Sanaka Successful single-balloon enteroscopic dilation of late anastomotic pancreaticojejunostomy stricture following Whipple procedure. *Pancreas* 2010; 39: 115-6 (letter).
607. Morgan KA, Adams DB. Solid tumors of the body and tail of the pancreas. *Surg Clin North Am* 2010; 90: 287-307.
608. Fujita T, Nakagohri T, Gotohda N, Takahashi S, Konishi M, Kojima M, Kinoshita T. Evaluation of the prognostic factors and significance of lymph node status in invasive ductal carcinoma of the body or tail of the pancreas. *Pancreas* 2010; 39: e48-54.
609. Yamamoto J, Saiura A, Koga R, Seki M, Katori M, Kato Y, Sakamoto Y, Kokudo N, Yamaguchi T. Improved survival of left-sided pancreas cancer after surgery. *Jpn J Clin Oncol* 2010; 40: 530-6.
610. Røsok BI, Marangos IP, Kazaryan AM, Rosseland AR, Buanes T, Mathisen O, Edwin B. Single-centre experience of laparoscopic pancreatic surgery. *Br J Surg* 2010; 97: 902-9.
611. Jayaraman S, Gonen M, Brennan MF, D'Angelica MI, DeMatteo RP, Fong Y, Jarnagin WR, Allen PJ. Laparoscopic distal pancreatectomy: evolution of a technique at a single institution. *J Am Coll Surg* 2010; 211: 503-9.
612. Kooby DA, Hawkins WG, Schmidt CM, Weber SM, Bentrem DJ, Gillespie TW, Sellers JB, Merchant NB, Scoggins CR, Martin RC 3rd, Kim HJ, Ahmad S, Cho CS, Parikh AA, Chu CK, Hamilton NA, Doyle CJ, Pinchot S, Hayman A, McClaine R, Nakeeb A, Staley CA, McMasters KM, Lillemoe KD.

- A multicenter analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? *J Am Coll Surg* 2010; 210: 779-85.
613. Newman NA, Lennon AM, Edil BH, Gilson MM, Giday SA, Canto MI, Schulick RD, Makary MA. Preoperative endoscopic tattooing of pancreatic body and tail lesions decreases operative time for laparoscopic distal pancreatectomy. *Surgery* 2010; 148: 371-7.
614. Zhou W, Lv R, Wang X, Mou Y, Cai X, Herr I. Stapler vs suture closure of pancreatic remnant after distal pancreatectomy: a meta-analysis. *Am J Surg* 2010; 200: 529-36.
615. Eom BW, Yoon H, Han SS, Ryu KW, Lee JH, Kim SH, Lee KW, Park SJ, Kim YW. Laparoscopy-assisted distal gastrectomy combined with laparoscopic spleen-preserving distal pancreatectomy for the treatment of early gastric cancer with pancreatic cystic neoplasm. *J Laparoendosc Adv Surg Tech A* 2010; 20: 643-7.
616. Botwinick I, Schrope BA, Chabot JA. Distal pancreatectomy with en bloc celiac axis resection after neoadjuvant therapy for locally advanced pancreatic adenocarcinoma. *Pancreas* 2010; 39: 1111-3 (letter).
617. Sperti C, Berselli M, Pedrazzoli P. Distal pancreatectomy for body-tail pancreatic cancer: Is there a role for celiac axis resection? *Pancreatol* 2010; 10: 491-8.
618. Lee MK, Dinorcja J, Reavey PL, Holden MM, Genkinger JM, Lee JA, Schrope BA, Chabot JA, Allendorf JD. Pancreaticoduodenectomy can be performed safely in patients aged 80 years and older. *J Gastrointest Surg* 2010 Sep 8 [Epub ahead of print].
619. Oliverius M, Kala Z, Varga M, Gürlich R, Lanska V, Kubesova H. Radical surgery for pancreatic malignancy in the elderly. *Pancreatol* 2010; 10: 499-502.
620. Peros G, Giannopoulos GA, Christodoulou S, Konstantoudakis G, Petropoulou K, Sakorafas GH. Good results after major pancreatic resections in a middle-volume center. *Pancreas* 2010; 39: 411-4.
621. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, Kooby DA. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg* 2010; 210: 463-73.
622. Hashimoto Y, Traverso LW. Incidence of pancreatic anastomotic failure and delayed gastric emptying after pancreatoduodenectomy in 507 consecutive patients: use of a web-based calculator to improve homogeneity of definition. *Surgery* 2010; 147: 503-15.
623. Sanjay P, Fawzi A, Kull C, Polignano F, Tait, Iain IS. Impact of methicillin resistant *Staphylococcus aureus* (MRSA) infection on patient outcome after pancreatoduodenectomy (PD) – a cause for concern? *Pancreas* 2010; 39: 1211-4.
624. Kurahara H, Takao S, Shinchi H, Mataka Y, Maemura K, Sakoda M, Ueno S, Natsugoe S. Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) prevents postoperative delayed gastric emptying. *J Surg Oncol* 2010; 102: 615-9.
625. Welsch T, Borm M, Degrade L, Hinz U, Büchler MW, Wente MN. Evaluation of the International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. *Br J Surg* 2010; 97: 1043-50.
626. Gaujoux S, Cortes A, Couvelard A, Noullet S, Clavel L, Rebours V, Lévy P, Sauvanet A, Ruszniewski P, Belghiti J. Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. *Surgery* 2010; 148: 15-23.
627. Lee SE, Jang JY, Lim CS, Kang MJ, Kim SH, Kim MA, Kim SW. Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. *Ann Surg* 2010; 251: 932-6.

628. Moskovic DJ, Hodges SE, Wu MF, Brunicardi FC, Hilsenbeck SG, Fisher WE. Drain data to predict clinically relevant pancreatic fistula. *HPB* 2010; 12: 472-81.
629. Kah Heng CA, Salleh I, San TS, Ying F, Su-Ming T. Pancreatic fistula after distal pancreatectomy: incidence, risk factors and management. *ANZ J Surg* 2010; 80: 619-23.
630. Frozanpor F, Albiin N, Linder S, Segersvärd R, Lundell L, Arnelo U. Impact of pancreatic gland volume on fistula formation after pancreatic tail resection. *JOP* 2010; 11: 439-43.
631. Camerlo A, Turrini O, Marciano S, Sarran A, Berdah S, Delpero JR, Moutardier V. Delayed arterial hemorrhage after pancreaticoduodenectomy: is conservation of hepatic arterial flow vital? *Pancreas* 2010; 39: 260-2 (letter).
632. Kanda M, Takeda S, Yamada S, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Nakao A. Operative treatment of pancreatic ductal adenocarcinoma with extensive portal venous tumor embolism. *Pancreas* 2010; 39: 268-9 (letter).
633. Seeger M, Günther R, Hinrichsen H, Both M, Helwig U, Arlt A, Stelck B, Bräsen JH, Sipos B, Schafmayer C, Braun F, Bröring DC, Schreiber S, Hampe J. Chronic portal vein thrombosis: transcapsular hepatic collateral vessels and communicating ectopic varices. *Radiology* 2010 Sep 9 [Epub ahead of print].
634. Kanda M, Takeda S, Yamada S, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Nakao A.. Operative treatment of thrombotic occlusion of the portal vein immediately after pancreatectomy with portal vein resection. *Pancreas* 2009; 39: 265-6 (letter).
635. Breuer TG, Menge BA, Banasch M, Uhl W, Tannapfel A, Schmidt WE, Nauck MA, Meier JJ. Proinsulin levels in patients with pancreatic diabetes are associated with functional changes in insulin secretion rather than pancreatic beta-cell area. *Eur J Endocrinol* 2010; 163: 551-8.
636. Iwasaki Y, Sawada T, Kijima H, Kosuge T, Katoh M, Kita J, ShimodaM, Kubota K. Estimated glomerular filtration rate is superior to measured creatinine clearance for predicting postoperative renal dysfunction in patients undergoing pancreatoduodenectomy. *Pancreas* 2010; 39: 20-25.
637. Khe Tran TC, van Lanschot JJB, Bruno MJ, van Eijck CHJ. Functional changes after pancreatoduodenectomy: diagnosis and treatment. *Pancreatology* 2009; 9: 729-37.
638. McCluggage WG, Hurrell DP, Kennedy K. Metastatic carcinomas in the cervix mimicking primary cervical adenocarcinoma and adenocarcinoma in situ: report of a series of cases. *Am J Surg Pathol* 2010; 34: 735-41.
639. Kameda R, Ueno M, Kobayashi S, Miyagawa K, Okawa S, Morinaga S. A case of abdominal wall metastasis from pancreatic cancer. *Gan To Kagaku Ryoho* 2010; 37: 1149-52 (in Japanese).
640. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. *Cochrane Database Syst Rev* 2010; (10): CD008533
641. Shaw JM, Bornman PC, Krige JE, Stupart DA, Panieri E. Self-expanding metal stents as an alternative to surgical bypass for malignant gastric outlet obstruction. *Br J Surg* 2010; 97: 872-6.
642. Bang BW, Jeong S, Lee DH, Kim CH, Cho SG, Jeon YS. Curved planar reformatted images of MDCT for differentiation of biliary stent occlusion in patients with malignant biliary obstruction. *Am J Roentgenol* 2010; 194: 1509-14.
643. Tian Y, Wu SD, Chen YS, Chen CC. Transumbilical single-incision laparoscopic cholecystojejunostomy using conventional instruments: the first two cases. *J Gastrointest Surg* 2010; 14: 1429-33.
644. Onuma T, Yoshida Y, Yamamoto T, Kotsuji F. Diagnosis and management of pancreatic carcinoma during pregnancy. *Obstet Gynecol* 2010; 116 suppl 2: 518-20.

645. Turaga KK, Malafa MP, Jacobsen PB, Schell MJ, Sarr MG. Suicide in patients with pancreatic cancer. *Ancr* 2010 Sep 7 [Epub ahead of print].
646. Ding YZ, Cravero JD, Adrian K, Grippo P. Modeling pancreatic cancer in vivo: from xenograft and carcinogen-induced systems to genetically engineered mice. *Pancreas* 2010; 39: 283-92.
647. Chen XL, Ma Y, Wan Y, Duan LG. Experimental study of the safety of pancreas cryosurgery: the comparison of 2 different techniques of cryosurgery. *Pancreas* 2010; 39: 92-6.
648. Johnson CD, Berry DP, Harris S, Pickering RM, Davis C, George S, Imrie CW, Neoptolemos JP, Sutton R. An open randomized comparison of clinical effectiveness of protocol-driven opioid analgesia, celiac plexus block or thoracoscopic splanchnicectomy for pain management in patients with pancreatic and other abdominal malignancies. *Pancreatol* 2009; 9: 755-63.
649. Hsu YC, Yen HH, Chen YY, Soon MS. Successful endoscopic sclerotherapy for cholecystojejunostomy variceal bleeding in a patient with pancreatic head cancer. *World J Gastroenterol* 2010; 16: 123-5.
650. Wang J, Su T, Jia NY, Wang J, Wang CG, Wang SG, Qian Y, Han XI. Computed tomographic and magnetic resonance imaging presentations of pancreatitis maldiagnosed as pancreatic carcinoma. *Pancreas* 2010; 39: 262-4 (letter).
651. Renouf D, Moore M. Evolution of systemic therapy for advanced pancreatic cancer. *Expert Rev Anticancer Ther* 2010; 10: 529-40.
652. Di Marco M, Di Ciglia R, Macchini M, Nobili E, Vecchiarelli S, Brandi G, Biasco G. Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? *Oncol Rep* 2010; 23: 1183-92.
653. Nugent FW, Stuart K. Adjuvant and neoadjuvant therapy in curable pancreatic cancer. *Surg Clin North Am* 2010; 90: 323-39.
654. Huguet F. Is there still a place for radiotherapy for the treatment of pancreatic cancers. *Presse Med* 2010; 39: 645-52 (in French).
655. Klapdor R, Bahlo M, Babinski A, Klapdor S. CA19-9 serum concentrations – analysis of the serum kinetics during first-line therapy of pancreatic cancer in relation to overall survival. *Anticancer res* 2010; 30: 1869-74.
656. Haas M, Laubender RP, Stieber P, Holdenrieder S, Bruns CJ, Wilkowski R, Mansmann U, Heinemann V, Boeck S. Prognostic relevance of CA 19-9, CEA, CRP, and LDH kinetics in patients treated with palliative second-line therapy for advanced pancreatic cancer. *Tumour Biol* 2010; 31: 351-7.
657. Lal A, Christians K, Evans DB. Management of borderline resectable pancreatic cancer. *Surg Oncol Clin N Am* 2010; 19: 359-70.
658. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, Xu N, Cooper H, Benson AB 3rd. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. *J Surg Oncol* 2010; 101: 587-92.
659. Gillen S, Schuster T, Meyer zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; 7: e1000267.
660. Choi M, Heilbrun LK, Venkatramamoorthy R, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using 18F-fluorodeoxyglucose positron emission tomography to monitor clinical outcomes in patients treated with neoadjuvant chemo-radiotherapy for locally advanced pancreatic cancer. *Am J Clin Oncol* 2010; 33: 257-61.

661. Sahora K, Kuehrer I, Eisenhut A, Akan B, Koellblinger C, Goetzinger P, Teleky B, Jakesz R, Peck-Radosavljevic M, Ba'ssalamah A, Zielinski C, Gnant M. NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. *Surgery* 2010 Sep 2 [Epub ahead of print].
662. Turrini O, Ychou M, Moureau-Zabotto L, Rouanet P, Giovannini M, Moutardier V, Azria D, Delpero JR, Viret F. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: New neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol* 2010; 36: 987-92.
663. Kruth J, Nissen J, Ernst T, Kripp M, Lukan N, Merx K, Hofmann WK, Hochhaus A, Hofheinz RD. Efficacy and safety of capecitabine in combination with docetaxel and mitomycin C in patients with pre-treated pancreatic, gallbladder, and bile duct carcinoma. *J Cancer Res Clin Oncol* 2010; 136: 1845-51.
664. Turrini O, Ychou M, Moureau-Zabotto L, Rouanet P, Giovannini M, Moutardier V, Azria D, Delpero JR, Viret F. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas. New neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol* 2010 Sep 7 [Epub ahead of print].
665. Hilbig A, Oettle H. Adjuvant therapy of pancreatic cancer. *Expert Rev Anticancer Ther* 2010; 10: 485-91.
666. Hsu CC, Herman JM, Corsini MM, Winter JM, Callister MD, Haddock MG, Cameron JL, Pawlik TM, Schulick RD, Wolfgang CL, Laheru DA, Farnell MB, Swartz MJ, Gunderson LL, Miller RC. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol* 2010; 174: 981-90.
667. Hristov B, Reddy S, Lin SH, Cameron JL, Pawlik TM, Hruban RH, Swartz MJ, Edil BH, Kemp C, Wolfgang CL, Herman JM. Outcomes of adjuvant chemoradiation after pancreaticoduodenectomy with mesenterico-portal vein resection for adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 2010; 76: 176-80.
668. Katz MH, Merchant NB, Brower S, Branda M, Posner MC, William Traverso L, Abrams RA, Picozzi VJ, Pisters PW; The American College of Surgeons Oncology Group. Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy for pancreatic cancer: results from the ACOSOG Z5031 trial. *Ann Surg* 2010 sep 1 [Epub ahead of print].
669. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010; 28: 4450-6.
670. Richards NG, Rittenhouse DW, Freydin B, Cozzitorto JA, Grenda D, Rui H, Gonye G, Kennedy EP, Yeo CJ, Brody JR, Witkiewicz AK. HuR status is a powerful marker for prognosis and response to gemcitabine-based chemotherapy for resected pancreatic ductal adenocarcinoma patients. *Ann Surg* 2010; 252: 499-505.
671. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; 304: 1073-81.
672. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010 Sep 13 [Epub ahead of print].

673. Matsuda M, Watanabe G, Hashimoto M, Sasaki K. Feasibility study of adjuvant chemotherapy with S-1 for pancreatic adenocarcinoma. *Gan To Kagaku Ryoho* 2010; 37: 655-8 (in Japanese).
674. Aiura K, Takahashi S, Matsui J, Ueda M, Kitagawa Y. Beneficial effects of 5-fluorouracil and heparin-based portal infusion chemotherapy combined with mitomycin C and cisplatin after curative resection of pancreatic cancer. *Pancreatol* 2010; 10: 250-8.
675. Ogawa K, Karasawa K, Ito Y, Ogawa Y, Jingu K, Onishi H, Aoki S, Wada H, Kokubo M, Etoh H, Kazumoto T, Takayama M, Negoro Y, Nemoto K, Nishimura Y; JROSG Working Subgroup of Gastrointestinal Cancers. Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. *Int J Radiat Oncol Biol Phys* 2010; 77: 734-42.
676. McDade TP, Hill JS, Simons JP, Piperdi B, Ng SC, Zhou Z, Kadish SP, Fitzgerald TJ, Tseng JF. A national propensity-adjusted analysis of adjuvant radiotherapy in the treatment of resected pancreatic adenocarcinoma. *Cancer* 2010; 116: 3257-66.
677. Rwigema JC, Heron DE, Parikh SD, Zeh HJ 3rd, Moser JA, Bahary N, Ashby K, Burton SA. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer Sep 1* [Epub ahead of print].
678. Haas M, Laubender RP, Stieber P, Holdenrieder S, Bruns CJ, Wilkowski R, Mansmann U, Heinemann V, Boeck S. Prognostic relevance of CA 19-9, CEA, CRP, and LDH kinetics in patients treated with palliative second-line therapy for advanced pancreatic cancer. *Tumour Biol* 2010; 31: 351-7.
679. Bernhard J, Dietrich D, Glimelius B, Hess V, Bodoky G, Scheithauer W, Herrmann R. Estimating prognosis and palliation based on tumour marker CA 19-9 and quality of life indicators in patients with advanced pancreatic cancer receiving chemotherapy. *Br J Cancer* 2010; 103: 1318-24.
680. Mancuso A, Sacchetta S, Saletti PC, Tronconi C, Milesi L, Garassino M, Martelli O, Leone A, Zivi A, Cerbone L, Recine F, Sollami R, Labianca R, Cavalli F, Sternberg CN. Clinical and molecular determinants of survival in pancreatic cancer patients treated with second-line chemotherapy: results of an Italian/Swiss multicenter survey. *Anticancer Res* 2010; 30: 4289-95.
681. Cao YF, Wu LC, Tan AH, Liu LD, Liao C, Gao F. Meta-analysis of randomized trials: evaluation of benefit of gemcitabine-based molecular targeted therapy for inoperable pancreatic cancer. *Pancreas* 2010; 39: 253-5 (letter).
682. Hagmann W, Jesnowski R, Löhr JM. Interdependence of gemcitabine treatment, transporter expression, and resistance in human pancreatic carcinoma cells. *Neoplasia* 2010; 12: 740-7.
683. Nishida T, Tsutsui S, Yamamoto K, Konishi K, Hayashi Y, Iijima H, Tsujii M, Takeda Y, Kitagawa T, Yoshioka Y, Inoue T, Hayashi N. Phase I trial of gemcitabine dose escalation with concurrent radiotherapy for patients with locally advanced pancreatic cancer. *Pancreatol* 2010; 10: 60-65.
684. Tanaka H, Takamori H, Eto S, Ozaki N, Akaboshi S, Nakahara O, Ida S, Furuhashi S, Abe S, Horino K, Beppu T, Baba H. Acute liver injury with hepatic encephalopathy associated with gemcitabine administration for adjuvant chemotherapy in an HBV carrier with pancreatic cancer. *Gan To Kagaku Ryoho* 2010; 37: 1783-6 (in Japanese).
685. Wato M, Inaba T, Ishikawa H, Ishikawa S, Baba N, Miyoshi M, Senoh T, Nagano T, Takaguchi K, Watanabe S, Kawai K. A case of hemolytic uremic syndrome after adjuvant chemotherapy with gemcitabine in a patient with pancreatic cancer. *Nippon Shokakibyo Gakkai Zasshi* 2010; 107: 1676-85 (in Japanese).
686. Ishii H, Furuse J, Boku N, Okusaka T, Ikeda M, Ohkawa S, Fukutomi A, Hamamoto Y, Nakamura K, Fukuda H; JCOG Gastrointestinal Oncology Study Group. Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG0506. *Jpn J Clin Oncol* 2010; 40: 573-9.

687. Cham KK, Baker JH, Takhar KS, Flexman JA, Wong MQ, Owen DA, Yung A, Kozlowski P, Reinsberg SA, Chu EM, Chang CW, Buczkowski AK, Chung SW, Scudamore CH, Minchinton AI, Yapp DT, Ng SS. Metronomic gemcitabine suppresses tumour growth, improves perfusion, and reduces hypoxia in human pancreatic ductal adenocarcinoma. *Br J Cancer* 2010; 103: 52-60.
688. Lipton A, Campbell-Baird C, Witters L, Harvey H, Ali S. Phase II trial of gemcitabine, irinotecan, and celecoxib in patients with advanced pancreatic cancer. *J Clin Gastroenterol* 2010; 44: 286-8.
689. Xie DR, Yang Q, Chen DL, Jiang ZM, Bi ZF, Ma W, Zhang YD. Gemcitabine-based cytotoxic doublets chemotherapy for advanced pancreatic cancer: updated subgroup meta-analyses of overall survival. *Jpn J Clin Oncol* 2010; 40: 432-41.
690. Reni M, Sartori N, Mambrini A, Berardi R, Passardi A, Milella M, Cereda S, Tronconi MC, Aprile G, Cordio S, Pasetto LM, Rognone A, Pederzoli P, Falconi M. An Italian study on treatment trends and outcomes of patients with stage III pancreatic adenocarcinoma in the gemcitabine era: is it time to change? *Anticancer Drugs* 2010; 21: 459-64.
691. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Carteni G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F; Gruppo Oncologico Italia Meridionale (GOIM); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010; 28: 1645-51.
692. Reni M, Sartori N, Mambrini A, Berardi R, Passardi A, Milella M, Cereda S, Tronconi MC, Aprile G, Cordio S, Pasetto LM, Rognone A, Pederzoli P, Falconi M. An Italian study on treatment trends and outcomes of patients with stage III pancreatic adenocarcinoma in the gemcitabine era: is it time to change? *Anticancer Drugs* 2010; 21: 459-64.
693. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Carteni G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F; Gruppo Oncologico Italia Meridionale (GOIM); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010; 28: 1645-51.
694. Nakachi K, Furuse J, Kinoshita T, Kawashima M, Ishii H, Ikeda M, Mitsunaga S, Shimizu S. A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 527-34.
695. Fukui H, Kou C, Matsumoto T, Matsumoto M. S-1+gemcitabine (GEM) therapy effective in a case of pancreatic body cancer with multiple liver metastasis. *Gan To Kagaku Ryoho* 2010 Sep 37: 1775-8 (in Japanese).
696. Miyagawa K, Yata Y, Yamaoka N, Sagara Y. A case of complete response (CR) to combination therapy of S-1 and gemcitabine (GEM) for unresectable pancreatic cancer. *Gan To Kagaku Ryoho* 2010; 37: 1145-7 (in Japanese).
697. Kurihara T, Kobayashi M, Kogo M, Yoneyama K, Ito N, Sunaga T, Konishi K, Imawari M, Tobe T, Kiuchi Y. Cost-effectiveness analysis of chemotherapy with GEM or S-1 for patients with non-resectable pancreatic cancer. *Gan To Kagaku Ryoho* 2010; 37: 659-64 (in Japanese).
698. Strumberg D, Schultheis B, Scheulen ME, Hilger RA, Krauss J, Marschner N, Lordick F, Bach F, Reuter D, Edler L, Mross K. Safety, efficacy and pharmacokinetics of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer. *Int J Clin Pharmacol Ther* 2010; 48: 473-5.

699. Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fenoglio-Preiser CM, Abbruzzese JL, Blanke CD. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; 28: 3605-10.
700. Moinpour CM, Vaught NL, Goldman B, Redman MW, Philip PA, Millwood B, Lippman SM, Seay TE, Flynn PJ, O'Reilly EM, Rowland KM, Wong RP, Benedetti J, Blanke CD. Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a phase III study comparing gemcitabine plus cetuximab versus gemcitabine as first-line therapy in patients with advanced pancreas cancer. *J Clin Oncol* 2010; 28: 3611-6.
701. Dahan L, Bonnetain F, Ychou M, Mityr E, Gasmi M, Raoul JL, Cattan S, Phelip JM, Hammel P, Chauffert B, Michel P, Legoux JL, Rougier P, Bedenne L, Seitz JF; Fédération Francophone de Cancérologie Digestive. Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301). *Gut* 2010; 59: 1527-34.
702. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; 28: 3617-22.
703. Cheon EC, Small W Jr, Strouch MJ, Krantz SB, Rademaker A, Mulcahy MF, Benson AB, Bentrem DJ, Talamonti MS. The effects of bevacizumab on postoperative complications in patients undergoing colorectal and pancreatic cancer resection. *J Surg Oncol* 2010 Sep 1 [Epub ahead of print].
704. da Cunha Santos G, Dhani N, Tu D, Chin K, Ludkovski O, Kamel-Reid S, Squire J, Parulekar W, Moore MJ, Tsao MS. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: national Cancer Institute of Canada Clinical Trials Group Study PA.3. *Cancer* 2010 Sep 7 [Epub ahead of print].
705. Mityr E, Hammel P, Deplanque G, Mornex F, Levy P, Seitz JF, Moussy A, Kinet JP, Hermine O, Rougier P, Raymond E. Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 395-403.
706. Mityr E, Hammel P, Deplanque G, Mornex F, Levy P, Seitz JF, Moussy A, Kinet JP, Hermine O, Rougier P, Raymond E. Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 395-403.
707. Cohen SJ, Zalupski MM, Modiano MR, Conkling P, Patt YZ, Davis P, Dorr RT, Boytim ML, Hersh EM. A phase I study of imexon plus gemcitabine as first-line therapy for advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 287-94.
708. Chiorean EG, Dragovich T, Hamm J, Barrios CH, Gorini CF, Langmuir VK, Kroll S, Jung DT, Tidmarsh GT, Loehrer PJ. A phase 2 trial of glufosfamide in combination with gemcitabine in chemotherapy-naïve pancreatic adenocarcinoma. *Am J Clin Oncol* 2010; 33: 111-6.
709. Girard N, Mornex F, Bossard N, Ychou M, Chauffert B, Wautot V. Estimating optimal dose of twice-weekly gemcitabine for concurrent chemoradiotherapy in unresectable pancreatic carcinoma: mature results of GEMRT-01 Phase I trial. *Int J Radiat Oncol Biol Phys* 2010; 77: 1426-32.
710. Zhao H, Yang G, Wang D, Yu X, Zhang Y, Zhu J, Ji Y, Zhong B, Zhao W, Yang Z, Aziz F. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. *Anticancer Drugs* 2010; 21: 447-52.
711. Lipton A, Campbell-Baird C, Witters L, Harvey H, Ali S. Phase II trial of gemcitabine, irinotecan, and celecoxib in patients with advanced pancreatic cancer. *J Clin Gastroenterol* 2010; 44: 286-8.

712. Sweeney CJ, Chiorean EG, Verschraegen CF, Lee FC, Jones S, Royce M, Tye L, Liau KF, Bello A, Chao R, Burris HA. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. *J Clin Oncol* 2010 Sep 13 [Epub ahead of print].
713. Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow D, Sawhney M, Brennan D, Callery M, Vollmer C. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010; 78: 735-42.
714. Jackson AS, Jain P, Watkins GR, Whitfield GA, Green MM, Valle J, Taylor MB, Dickinson C, Price PM, Saleem A. Efficacy and tolerability of limited field radiotherapy with concurrent capecitabine in locally advanced pancreatic cancer. *Clin Oncol (R Coll Radiol)* 2010; 22: 570-7.
715. Morganti AG, Picardi V, Ippolito E, Massaccesi M, Macchia G, Deodato F, Mattiucci GC, Caravatta L, Di Lullo L, Giglio G, Tambaro R, Mignogna S, Caprino P, Ingrosso M, Sofo L, Cellini N, Valentini V. Capecitabine based postoperative accelerated chemoradiation of pancreatic carcinoma. A dose-escalation study. *Acta Oncol* 2010; 49: 418-22.
716. Shukuya T, Yasui H, Boku N, Onozawa Y, Fukutomi A, Yamazaki K, Taku K, Kojima T, Machida N. Weekly paclitaxel after failure of gemcitabine in pancreatic cancer patients with malignant ascites: a retrospective study. *Jpn J Clin Oncol* 2010; 40: 1135-8.
717. Saif MW, Syrigos K, Penney R, Kaley K. Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study. *Anticancer Res* 2010; 30: 2905-9.
718. de la Fouchardière C, Négrier S, Labrosse H, Martel Lafay I, Desseigne F, Méeus P, Tavan D, Petit-Laurent F, Rivoire M, Pérol D, Carrie C. Phase I study of daily irinotecan as a radiation sensitizer for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010; 77: 409-13.
719. Oh SY, Kim HJ, Kim TH, Lee GW, Kim HG, Jeong CY, Kwon HC, Kang JH. Pilot study of irinotecan/oxaliplatin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil- refractory pancreatic cancer. *Invest New Drugs* 2010; 28: 343-9.
720. Todaka A, Fukutomi A, Boku N, Onozawa Y, Hironaka S, Yasui H, Yamazaki K, Taku K, Machida N, Sakamoto T, Tomita H. S-1 monotherapy as second-line treatment for advanced pancreatic cancer after gemcitabine failure. *Jpn J Clin Oncol* 2010; 40: 567-72.
721. Morishima K, Hyodo M, Nihei Y, Sata N, Yasuda Y. A case of acinar cell carcinoma of pancreas with liver metastases treated effectively by S-1. *Gan To Kagaku Ryoho* 2010; 37: 127-9 (in Japanese).
722. Nakai Y, Isayama H, Sasaki T, Sasahira N, Ito Y, Kogure H, Togawa O, Matsubara S, Arizumi T, Yagioka H, Yashima Y, Kawakubo K, Mizuno S, Yamamoto K, Hirano K, Tsujino T, Ijichi H, Tateishi K, Toda N, Tada M, Omata M, Koike K. Impact of S-1 on the survival of patients with advanced pancreatic cancer. *Pancreas* 2010; 39: 989-93.
723. Nakai Y, Isayama H, Sasaki T, Sasahira N, Kogure H, Hirano K, Tsujino T, Ijichi H, Tateishi K, Tada M, Omata M, Koike K. Impact of S-1 in patients with gemcitabine-refractory pancreatic cancer in Japan. *Jpn J Clin Oncol* 2010; 40: 774-80.
724. Hisama S, Kimura M, Nishimura T, Matsushita H, Okamura S, Saitoh S, Shimokawa Y, Arakawa A, Toyama H, Tanaka Y. A case of pancreatic cancer treated by gemcitabine with sequential radiotherapy. *Gan To Kagaku Ryoho* 2010; 37: 1337-9 (in Japanese).
725. Nakai Y, Isayama H, Sasaki T, Sasahira N, Ito Y, Kogure H, Togawa O, Matsubara S, Arizumi T, Yagioka H, Yashima Y, Kawakubo K, Mizuno S, Yamamoto K, Hirano K, Tsujino T, Ijichi H, Tateishi K, Toda N, Tada M, Omata M, Koike K. Impact of S-1 on the survival of patients with advanced pancreatic cancer. *Pancreas* 2010; 39: 989-93.
726. Ishii Y, Suzuki S, Takahashi Y, Takayama T, Asai S. Can the 2-¹³C-uracil breath test be used to predict the effect of the antitumor drug S-1? *Cancer Chemother Pharmacol* 2010; 66: 333-43.

727. Liu L, Cao Y, Tan A, Liao C, Gao F. Cetuximab-based therapy versus non-cetuximab therapy for advanced cancer: a meta-analysis of 17 randomized controlled trials. *Cancer Chemother Pharmacol* 2010; 65: 849-61.
728. Gebbia V, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-Fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. *Am J Clin Oncol* 2010; 33: 461-4.
729. Giroux V, Dagorn JC, Iovanna JL. A review of kinases implicated in pancreatic cancer. *Pancreatol* 2009; 9: 738-54.
730. Yu X, Zhang Y, Chen C, Yao Q, Li M. Targeted drug delivery in pancreatic cancer. *Biochim Biophys Acta* 2010; 1805: 97-104.
710. Sweeney CJ, Chiorean EG, Verschraegen CF, Lee FC, Jones S, Royce M, Tye L, Liau KF, Bello A, Chao R, Burris HA. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. *J Clin Oncol* 2010; 28: 4513-20.
732. Ko AH, Venook AP, Bergsland EK, Kelley RK, Korn WM, Dito E, Schillinger B, Scott J, Hwang J, Tempero MA. A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 1051-7.
733. Lassen U, Molife LR, Sorensen M, Engelholm SA, Vidal L, Sinha R, Penson RT, Buhl-Jensen P, Crowley E, Tjornelund J, Knoblauch P, de Bono JS. A phase I study of the safety and pharmacokinetics of the histone deacetylase inhibitor belinostat administered in combination with carboplatin and/or paclitaxel in patients with solid tumours. *Br J Cancer* 2010; 103: 12-7.
734. Lam AP, Sparano JA, Vinciguerra V, Ocean AJ, Christos P, Hochster H, Camacho F, Goel S, Mani S, Kaubisch A. Phase II study of paclitaxel plus the protein kinase C inhibitor bryostatin-1 in advanced pancreatic carcinoma. *Am J Clin Oncol* 2010; 33: 121-4.
735. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA. Phase 2 trial of single agent ipilimumab (Anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; Sept 13 [Epub ahead of print].
736. Nakai Y, Isayama H, Ijichi H, Sasaki T, Sasahira N, Hirano K, Kogure H, Kawakubo K, Yagioka H, Yashima Y, Mizuno S, Yamamoto K, Arizumi T, Togawa O, Matsubara S, Tsujino T, Tateishi K, Tada M, Omata M, Koike K. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. *Br J Cancer* 2010; 103: 1644-8.
737. Gillmore R, Laurence V, Raouf S, Tobias J, Blackman G, Meyer T, Goodchild K, Collis C, Bridgewater J. Chemoradiotherapy with or without induction chemotherapy for locally advanced pancreatic cancer: a UK multi-institutional experience. *Clin Oncol (R Coll Radiol)* 2010; 22: 564-9.
738. Didolkar MS, Coleman CW, Brenner MJ, Chu KU, Olexa N, Stanwyck E, Yu A, Neerchal N, Rabinowitz S. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma. Results of first 85 patients. *J Gastrointest Surg* 2010 Sep 14 [Epub ahead of print].
739. Shen ZT, Wu XH, Li B, Wang L, Zhu XX. Preliminary efficacy of CyberKnife radiosurgery for locally advanced pancreatic cancer. *Chin J Cancer* 2010; 29: 802-9.
740. Miyamoto DT, Mamon HJ, Ryan DP, Willett CG, Ancukiewicz M, Kobayashi WK, Blaszkowsky L, Fernandez-del Castillo C, Hong TS. Outcomes and tolerability of chemoradiation therapy for pancreatic cancer patients aged 75 years or older. *Int J Radiat Oncol Biol Phys* 2010; 77: 1171-7.
741. Ogawa K, Shibuya H, Uchida N, Onishi H, Okuno Y, Myojin M, Kobayashi M, Ogawa Y, Kanesaka N, Shibuya K, Tokumaru S, Sasamoto R, Karasawa K, Nemoto K, Nishimura Y. Postoperative external beam radiotherapy for resected pancreatic adenocarcinoma: impact of chemotherapy on local control and survival. *Anticancer Res* 2010; 30: 2959-67.

742. Ogawa K, Ito Y, Karasawa K, Ogawa Y, Onishi H, Kazumoto T, Shibuya K, Shibuya H, Okuno Y, Nishino S, Ogo E, Uchida N, Karasawa K, Nemoto K, Nishimura Y. Patterns of radiotherapy practice for pancreatic cancer in Japan: results of the Japanese Radiation Oncology Study Group (JROSG) survey. *Int J Radiat Oncol Biol Phys* 2010; 77: 743-50.
743. Murphy JD, Christman-Skieller C, Kim J, Dieterich S, Chang DT, Koong AC. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010; 78: 1420-6.
744. Eppinga W, Lagerwaard F, Verbakel W, Slotman B, Senan S. Volumetric modulated arc therapy for advanced pancreatic cancer. *Strahlenther Onkol* 2010; 186: 382-7.
745. Pezzilli R, Serra C, Ricci C, Casadei R, Monari F, D'Ambra M, Minni F. Radiofrequency ablation for advanced ductal pancreatic carcinoma. Is this approach beneficial for our patients? A systematic review. *Pancreas* 2011; 40: 163-4.
746. Deguchi T, Tanemura M, Miyoshi E, Nagano H, Machida T, Ohmura Y, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Ito T, Mori M, Doki Y, Sawa Y. Increased immunogenicity of tumor-associated antigen, mucin 1, engineered to express alpha-gal epitopes: a novel approach to immunotherapy in pancreatic cancer. *Cancer Res* 2010; 70: 5259-69.
747. Yanagimoto H, Shiomi H, Satoi S, Mine T, Toyokawa H, Yamamoto T, Tani T, Yamada A, Kwon AH, Komatsu N, Itoh K, Noguchi M. A phase II study of personalized peptide vaccination combined with gemcitabine for non-resectable pancreatic cancer patients. *Oncol Rep* 2010; 24: 795-801.
748. Li D, Abbruzzese JL. New strategies in pancreatic cancer: emerging epidemiologic and therapeutic concepts. *Clin Cancer Res* 2010; 16: 4313-8.
749. Orsi F, Zhang L, Arnone P, Orgera G, Bonomo G, Vigna PD, Monfardini L, Zhou K, Chen W, Wang Z, Veronesi U. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. *Am J Roentgenol* 2010; 195: W245-52.
750. Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Arch Pharm (Weinheim)* 2010; 343: 489-99.
751. Banerjee S, Kong D, Azmi AS, Wang Z, Ahmad A, Sethi S, Sarkar FH. Restoring sensitivity to oxaliplatin by a novel approach in gemcitabine resistant pancreatic cancer cells in vitro and in vivo. *Int J Cancer* 2010 Sep 7 [Epub ahead of print].
752. Fonsatti E, Maio M, Altomonte M, Hersey P. Biology and clinical applications of CD40 in cancer treatment. *Semin Oncol* 2010; 37: 517-23.
753. Fukamachi T, Chiba Y, Wang X, Saito H, Tagawa M, Kobayashi H. Tumor specific low pH environments enhance the cytotoxicity of lovastatin and cantharidin. *Cancer Lett* 2010; 297: 182-9.
754. Singh S, Srivastava SK, Bhardwaj A, Owen LB, Singh AP. CXCL12-CXCR4 signalling axis confers gemcitabine resistance to pancreatic cancer cells: a novel target for therapy. *Br J Cancer* 2010; 103: 1671-9.
755. Mohanty AK, Dilnawaz F, Mohanty C, Sahoo SK. Etoposide-loaded biodegradable amphiphilic methoxy (poly ethylene glycol) and poly (epsilon caprolactone) copolymeric micelles as drug delivery vehicle for cancer therapy. *Drug Deliv* 2010; 17: 330-42.
756. Jöst E, Roos WP, Kaina B, Schmidberger H. Response of pancreatic cancer cells treated with interferon-alpha or beta and co-exposed to ionising radiation. *Int J Radiat Biol* 2010; 86: 732-41.
757. Glazer ES, Massey KL, Zhu C, Curley SA. Pancreatic carcinoma cells are susceptible to noninvasive radio frequency fields after treatment with targeted gold nanoparticles. *Surgery* 2010; 148: 319-24.

758. Chabot JA, Tsai WY, Fine RL, Chen C, Kumah CK, Antman KA, Grann VR. Pancreatic proteolytic enzyme therapy compared with gemcitabine-based chemotherapy for the treatment of pancreatic cancer. *J Clin Oncol* 2010; 28: 2058-63.
759. Dongbin L, Fei L, Werner JB, Andersson R. Intraductal papillary mucinous neoplasms of the pancreas: diagnosis and management. *Eur J Gastroenterol Hepatol* 2010; 22: 1029-38.
760. Allen PJ. The management of intraductal papillary mucinous neoplasms of the pancreas. *Surg Oncol Clin N Am* 2010; 19: 297-310.
761. Augustin T, Vandermeer TJ. Intraductal papillary mucinous neoplasm: a clinicopathologic review. *Surg Clin North Am* 2010; 90: 377-98.
762. Sadakari Y, Ohuchida K, Nakata K, Ohtsuka T, Aishima S, Takahata S, Nakamura M, Mizumoto K, Tanaka M. Invasive carcinoma derived from the nonintestinal type intraductal papillary mucinous neoplasm of the pancreas has a poorer prognosis than that derived from the intestinal type. *Surgery* 2010; 147: 812-7.
763. Thosani N; Dasari CS, Bhutani MS, Raimondo M, Guha S. Molecular pathogenesis of intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; 39: 1129-33.
764. Hayashi A, Aishima S, Miyasaka Y, Nakata K, Morimatsu K, Oda Y, Nagai E, Oda Y, Tanaka M, Tsuneyoshi M. Pcd4 expression in intraductal papillary mucinous neoplasm of the pancreas: its association with tumor progression and proliferation. *Hum Pathol* 2010; 41: 1507-15.
765. Ikenaga N, Ohuchida K, Mizumoto K, Yu J, Kayashima T, Hayashi A, Nakata K, Tanaka M. Characterization of CD24 expression in intraductal papillary mucinous neoplasms and ductal carcinoma of the pancreas. *Hum Pathol* 2010; 41: 1466-74.
766. Miyasaka Y, Nagai E, Ohuchida K, Nakata K, Hayashi A, Mizumoto K, Tsuneyoshi M, Tanaka M. CD44v6 expression in intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; 39: 31-5.
767. Nakata K, Nagai E, Ohuchida K, Hayashi A, Miyasaka Y, Aishima S, Oda Y, Mizumoto K, Tanaka M, Tsuneyoshi M. S100P is a novel marker to identify intraductal papillary mucinous neoplasms. *Hum Pathol* 2010; 41: 824-31.
768. Takasu N, Kimura W, Moriya T, Hirai I, Takeshita A, Kamio Y, Nomura T. Intraductal papillary-mucinous neoplasms of the gastric and intestinal types may have less malignant potential than the pancreatobiliary type. *Pancreas* 2010; 39: 604-10.
769. Correa-Gallego C, Ferrone CR, Thayer SP, Wargo JA, Warshaw AL, Fernández-del Castillo C. Incidental pancreatic cysts: do we really know what we are watching? *Pancreatology* 2010; 10: 144-50.
770. Shin SH, Han DJ, Park KT, Kim YH, Park JB, Kim SC. Validating a simple scoring system to predict malignancy and invasiveness of intraductal papillary mucinous neoplasms of the pancreas. *World J Surg* 2010; 34: 776-83.
771. Yamada Y, Mori H, Matsumoto S, Hijiya N, Hongo N, Moriyama M. Invasive carcinomas originating from intraductal papillary mucinous neoplasms of the pancreas: conspicuity and primary sites of the solid masses on triple-phase dynamic CT imaging. *Abdom Imaging* 2010; 35: 181-8.
772. Mori H. New insight of pancreatic imaging: from "unexplored" to "explored". *Abdom Imaging* 2010; 35: 130-3.
773. Cheon YK, Cho YD, Jeon SR, Moon JH, Jeong SW, Hur KY, Jin SY, Lee JS. Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. *Am J Gastroenterol* 2010; 105: 1963-9.

774. Shimamoto T, Tani M, Kawai M, Hirono S, Ina S, Miyazawa M, Shimizu A, Uchiyama K, Yokoyama S, Tsutsumi M, Yamaue H. MUC1 is a useful molecular marker for malignant intraductal papillary mucinous neoplasms in pancreatic juice obtained from endoscopic retrograde pancreatography. *Pancreas* 2010; 39: 879-83.
775. Nakajima Y, Yamada T, Sho M. Malignant potential of intraductal papillary mucinous neoplasms of the pancreas. *Surg Today* 2010; 40: 816-24.
776. Tanno S, Nakano Y, Sugiyama Y, Nakamura K, Sasajima J, Koizumi K, Yamazaki M, Nishikawa T, Mizukami Y, Yanagawa N, Fujii T, Obara T, Okumura T, Kohgo Y. Incidence of synchronous and metachronous pancreatic carcinoma in 168 patients with branch duct intraductal papillary mucinous neoplasm. *Pancreatology* 2010; 10: 173-8.
777. Fujii T, Kato K, Kodera Y, Kanda M, Nagai S, Yamada S, Kanzaki A, Sugimoto H, Nomoto S, Takeda S, Morita S, Nakamura S, Nakao A. Prognostic impact of pancreatic margin status in the intraductal papillary mucinous neoplasms of the pancreas. *Surgery* 2010; 148: 285-90.
778. Wasif N, Bentrem DJ, Farrell JJ, Ko CY, Hines OJ, Reber HA, Tomlinson JS. Invasive intraductal papillary mucinous neoplasm versus sporadic pancreatic adenocarcinoma: a stage-matched comparison of outcomes. *Cancer* 2010; 116: 3369-77.
779. Uehara H, Ishikawa O, Ikezawa K, Kawada N, Inoue T, Takakura R, Takano Y, Tanaka S, Takenaka A. A natural course of main duct intraductal papillary mucinous neoplasm of the pancreas with lower likelihood of malignancy. *Pancreas* 2010; 39: 653-7.
780. Shin SS, Armao DM, Shah M, Kim YH, Lee CH, Rubinas T, Brubaker LM, Semelka RC. Management of branch-duct intraductal papillary mucinous neoplasms of the pancreas: observation with MR imaging. *Magn Reson Imaging* 2010 Sep 10 [Epub ahead of print].
781. Kanno A, Satoh K, Hirota M, Hamada S, Umino J, Itoh H, Masamune A, Asakura T, Shimosegawa T. Prediction of invasive carcinoma in branch type intraductal papillary mucinous neoplasms of the pancreas. *J Gastroenterol* 2010; 45: 952-9.
782. Tanno S, Nakan Y, Koizumi K, Sugiyama Y, Nakamura K, Sasajima J, Nishikawa T, Mizukami Y, Yanagawa N, Fujii T, Okumura T, Obara T, Kohgo Y. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. *Pancreas* 2010; 39: 36-40.
783. Sadakari Y, Ienaga J, Kobayashi K, Miyasaka Y, Takahata S, Nakamura M, Mizumoto K, Tanaka M. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. *Pancreas* 2010; 39: 232-6.
784. Jarry J, Belleannee G, Rault A, Sa Cunha A, Collet D. Can an intraductal papillary mucinous tumor be a potential indicator of concurrent adenocarcinoma of the pancreas? *JOP* 2010; 11: 55-7.
785. Ingkakul T, Sadakari Y, Ienaga J, Satoh N, Takahata S, Tanaka M. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg* 2010; 251: 70-5.
786. Turrini O, Waters JA, Schnelldorfer T, Lillemoe KD, Yiannoutsos CT, Farnell MB, Sarr MG, Schmidt CM. Invasive intraductal papillary mucinous neoplasm: predictors of survival and role of adjuvant therapy. *HPB* 2010; 12: 447-55.
787. Park J, Lee KT, Jang TH, Seo YW, Lee KH, Lee JK, Jang KT, Heo JS, Choi SH, Choi DW, Rhee JC. Risk factors associated with the postoperative recurrence of intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; 40: 42-5.
788. Calculli L, Pezzilli R, Brindisi C, Morabito R, Casadei R, Zompatori M. Pancreatic and extrapancreatic lesions in patients with intraductal papillary mucinous neoplasms of the pancreas: a single-centre experience. *Radiol Med* 2010; 115: 442-52.

789. Reid-Lombardo KM, Mathis KL, Wood CM, Harmsen WS, Sarr MG. Frequency of extrapancreatic neoplasms in intraductal papillary mucinous neoplasm of the pancreas: implications for management. *Ann Surg* 2010; 251: 64-9.
790. Pelletier AL, Hammel P, Rebours V, Couvelard A, Vullierme MP, Maire F, Hentic O, Aubert A, Sauvanet A, Levy P, Ruszniewski P. Acute pancreatitis in patients operated on for intraductal papillary mucinous neoplasms of the pancreas: frequency, severity, and clinicopathologic correlations. *Pancreas* 2010; 39: 658-61.
791. Harada R, Kawamoto H, Fukatsu H, Kato H, Hirao K, Kurihara N, Mizuno O, Ogawa T, Ishida E, Okada H, Yamamoto K, Yamamoto H. Nonprevention of post-endoscopic retrograde cholangiopancreatographic pancreatitis by pancreatic stent after aspiration of pure pancreatic juice in patients with intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; 39: 340-4.
792. Santi L, Renzuli M, Patti C, Capelli A, Moreiri ML. First case of 2 intraductal papillary mucinous tumors of both ventral and dorsal ducts in pancreas divisum. *Pancreas* 2010; 39: 110-1 (letter).
793. Swartz MJ, Hsu CC, Pawlik TM, Winter J, Hruban RH, Guler M, Schulick RD, Cameron JL, Laheru DA, Wolfgang CL, Herman JM. Adjuvant chemoradiotherapy after pancreatic resection for invasive carcinoma associated with intraductal papillary mucinous neoplasm of the pancreas. *Int J Radiat Oncol Biol Phys* 2010; 76: 839-44.
794. Lee MK, Dinorcica J, Pursell LJ, Holden MM, Tsai WY, Stevens PD, Goetz N, Grann VR, Chabot JA, Allendorf JD. Prophylactic pancreatectomy for intraductal papillary mucinous neoplasm does not negatively impact quality of life: a preliminary study. *J Gastrointest Surg* 2010 Sep 8 [Epub ahead of print].
795. Fritz S, Fernandez-del Castillo C, Iafrate AJ, Mino-Kenudson M, Neyhard N, LaFemina J, Stirman A, Warshaw AL, Thayer SP. Novel xenograft and cell line derived from an invasive intraductal papillary mucinous neoplasm of the pancreas give new insights into molecular mechanisms. *Pancreas* 2010; 39: 308-14.
796. Kamiyama H, Kamiyama M, Hong SM, Karikari CA, Lin MT, Borges MW, Griffith M, Young A, Norris-Kirby A, Lubek C, Mizuma M, Feldmann G, Shi C, Liang H, Goggins MG, Maitra A, Hruban RH, Eshleman JR. In vivo and in vitro propagation of intraductal papillary mucinous neoplasms. *Lab Invest* 2010; 90: 665-73.
797. Fritz S, Fernández-del Castillo C, Iafrate AJ, Mino-Kenudson M, Neyhard N, LaFemina J, Stirman A, Warshaw AL, Thayer SP. Novel xenograft and cell line derived from an invasive intraductal papillary mucinous neoplasm of the pancreas give new insights into molecular mechanisms. *Pancreas* 2010; 39: 308-14.
798. Buerke B, Heindel W, Wessling J. Differential diagnosis and radiological management of cystic pancreatic lesions. *Rofo* 2010; 182: 852-60 (in German).
799. Pausawasdi N, Scheiman JM. Pancreatic cystic lesions. *Curr Opin Gastroenterol* 2010; 26: 506-12.
800. Pausawasdi N, Heidt D, Kwon R, Simeone D, Scheiman J. Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. *Surgery* 2010; 147: 13-20.
801. Verbese JE, Munson JL. Pancreatic cystic neoplasms. *Surg Clin North Am* 2010; 90: 411-25.
802. Salvia R, Crippa S, Partelli S, Malleo G, Marcheggiani G, Bacchion M, Butturini G, Bassi C. Pancreatic cystic tumours: when to resect, when to observe. *Eur Rev Med Pharmacol Sci* 2010; 14: 395-406.
803. Williamson J, Westaby D, Stamp G, Jiao LR. A rare complex association of pancreatic cystadenoma. *Pancreas* 2010; 39: 264-5.

804. Haab BB, Porter A, Yue T, Li L, Scheiman J, Anderson MA, Barnes D, Schmidt CM, Feng Z, Simeone DM. Glycosylation variants of mucins and CEACAMs as candidate biomarkers for the diagnosis of pancreatic cystic neoplasms. *Ann Surg* 2010; 251: 937-45.
805. Hutchins G, Draganov PV. Diagnostic evaluation of pancreatic cystic malignancies. *Surg Clin North Am* 2010; 90: 399-410.
806. Beyer-Enke SA, Hocke M, Ignee A, Braden B, Dietrich CF. Contrast enhanced transabdominal ultrasound in the characterisation of pancreatic lesions with cystic appearance. *JOP* 2010; 11: 427-33.
807. Prasad S, Wilson J, Kalade A, Desmond P, Chen R. Endoscopic ultrasound of pancreatic cystic lesions. *ANZ J Surg* 2010; 80: 600-4.
807. Donahue TR, Hines OJ, Farrell JJ, Tomlinson JS, Eibl G, Reber HA. Cystic neoplasms of the pancreas: report of 114 cases. *Pancreas* 2010; 39: 1271-6.
809. Kim YC, Choi JY, Chung YE, Bang S, Kim MJ, Park MS, Kim KW. Comparison of MRI and endoscopic ultrasound in the characterization of pancreatic cystic lesions. *Am J Roentgenol* 2010; 195: 947-52.
810. Park WGU, Mascarenhas R, Palaez-Luna M, Smyrk TC, O'Kane D, Clain JE, Levy MJ, Pearson RK, Petersen BT, Topazian MD, Vege SS, Chari ST. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. *Pancreas* 2011; 40: 37-41.
811. Rogart JN, Loren DE, Singu BS, Kowalski TE. Cyst wall puncture and aspiration during EUS-guided fine needle aspiration may increase the diagnostic yield of mucinous cysts of the pancreas. *J Clin Gastroenterol* 2010 Sep 2 [Epub ahead of print].
812. Thosani N, Thosani S, Qiao W, Fleming JB, Bhutani MS, Guha S. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Dis Scin* 2010; 55: 2756-66.
813. Morris-Stiff G, Lentz G, Chalikonda S, Johnson M, Biscotti C, Stevens T, Matthew Walsh R. Pancreatic cyst aspiration analysis for cystic neoplasms: mucin or carcinoembryonic antigen--which is better? *Surgery* 2010; 148: 638-44.
814. Nguyen BN, Edgecombe A, Gomes M, Soucy G, Marginean CE, Mai KT. Comparative immunohistochemical study of the stroma of serous and mucinous cystic neoplasms. Possible histopathogenetic relationship of the 2 entities. *Pancreas* 2011; 40: 30-6.
815. Theruvath TP, Morgan KA, Adams DB. Mucinous cystic neoplasms of the pancreas: how much preoperative evaluation is needed? *Am Surg* 2010; 76: 812-7.
816. Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukusma N, Ohike N, Shimizu M, Hatori T, Nobukawa B, Hifumi M, Kobayashi Y, Tobita K, Tanno S, Sugiyama M, Miyasaka Y, Nakagohri T, Yamaguchi T, Hanada K, Abe H, Tada M, Fujita N, Tanaka M. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma. A multi-institutional study of the Japan Pancreas Society. *Pancreas* 2011; 40: 52-4.
817. Cao W, Adley BP, Liao J, Lin X, Talamonti M, Bentrem DJ, Rao SM, Yang GY. Mucinous nonneoplastic cyst of the pancreas: apomucin phenotype distinguishes this entity from intraductal papillary mucinous neoplasm. *Hum Pathol* 2010; 41: 513-21.
818. Erdogan D, Kloek J, Lamers WH, Offerhaus GJ, Busch OR, Gouma DJ, van Gulik TM. Mucinous cystadenomas in liver: management and origin. *Dig Surg* 2010; 27: 19-23.
819. Safo AO, Pambuccian SE. Pancreatic manifestations of von Hippel-Lindau disease. *Arch Pathol Lab Med* 2010; 134: 1080-3.

820. Davenport MS, Caoili EM, Cohan RH, Hoff CN, Ellis JH. Pancreatic manifestations of von Hippel-Lindau disease-effect of imaging on clinical management. *J Comput Assist Tomogr* 2010; 34: 517-22.
821. Neuzillet C, Vullierme MP, Couvelard A, Sauvanet A, Levy P, Richard S, Ruszniewski P, Hammel P. Difficult diagnosis of atypical cystic pancreatic lesions in von Hippel-Lindau disease. *J Comput Assist Tomogr* 2010; 34: 140-5.
822. Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. *Ann Surg Oncol* 2010; 17: 991-7.
823. Hsu HP, Shan YS, Jin YT, Lai MD, Lin PW. Loss of E-cadherin and beta-catenin is correlated with poor prognosis of ampullary neoplasms. *J Surg Oncol* 2010; 101: 356-62.
824. Bendixen M, Dahl S, Fristrup C, Mortensen MB. Evaluation of curative and palliative treatment of duodenal adenocarcinoma. *Ugeskr Laeger* 2010; 172: 1376-9 (in Danish).
825. Egorov VI, Butkevich AC, Sazhin AV, Yashina NI, Bogdanov SN. Pancreas-preserving duodenal resections with bile and pancreatic duct replantation for duodenal dystrophy. Two case reports. *JOP* 2010; 11: 446-52.
826. Ohtake S, Kobayashi N, Kato S, Kubota K, Endo I, Inayama Y, Nakajima A. Duodenal gastrointestinal stromal tumor resembling a pancreatic neuroendocrine tumor in a patient with neurofibromatosis type I (von Recklinghausen's disease): a case report. *J Med Case Reports* 2010; 8: 302.
827. Hur S, Han JK, Kim MA, Bae JM, Choi BI. Brunner's gland hamartoma: computed tomographic findings with histopathologic correlation in 9 cases. *J Comput Assist Tomogr* 2010; 34: 543-7.
828. Park HJ, Jang KT, Heo JS, Choi YL, Han J, Kim SH. A potential case of intraductal tubulopapillary neoplasms of the bile duct. *Pathol Int* 2010; 60: 630-5.
829. Kim K, Chie EK, Jang JY, Kim SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. Is duodenal invasion a relevant prognosticator in patients undergoing adjuvant chemoradiotherapy for distal common bile duct cancer? *Int J Radiat Oncol Biol Phys* 2010; 77: 1186-90.
830. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010; 103: 469-74.
831. Dahl S, Bendixen M, Fristrup CW, Mortensen MB. Treatment outcomes for patients with papilla of Vater cancer. *Ugeskr Laeger* 2010; 172: 1361-5 (in Danish).
832. Ohike N, Kim GE, Tajiri T, Krasinskas A, Basturk O, Coban I, Bandyopadhyay S, Morohoshi T, Goodman M, Kooby DA, Sarmiento JM, Adsay NV. Intra-ampullary papillary-tubular neoplasm (IAPN): characterization of tumoral intraepithelial neoplasia occurring within the ampulla: a clinicopathologic analysis of 82 cases. *Am J Surg Pathol* 2010; 34: 1731-48.
833. Chung YE, Kim MJ, Park MS, Choi JY, Kim H, Kim SK, Lee M, Kim HJ, Choi JS, Song SY, Kim KW. Differential features of pancreatobiliary- and intestinal-type ampullary carcinomas at MR imaging. *Radiology* 2010; 257: 284-93.
834. Mansfield A, Tafur A, Smithedajkul P, Corsini M, Quevedo F, Miller R. Mayo Clinic experience with very rare exocrine pancreatic neoplasms. *Pancreas* 2010; 39: 972-5.
835. Butte JM, Brennan MF, Gönen M, Tang LH, D'Angelica MI, Fong Y, Dematteo RP, Jarnagin WR, Allen PJ. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. *J Gastrointest Surg* 2010 Sep 8 [Epub ahead of print].
836. Stoita A, Earls P, Williams D. Pancreatic solid pseudopapillary tumours - EUS FNA is the ideal tool for diagnosis. *ANZ J Surg* 2010; 80: 615-8.

837. Chang H, Gong Y, Xu J, Su Z, Qin C, Zhang Z. Clinical strategy for the management of solid pseudopapillary tumor of the pancreas: aggressive or less? *Int J Med Sci* 2010; 7: 309-13.
838. Deshpande V, Oliva E, Young RH. Solid pseudopapillary neoplasm of the ovary: a report of 3 primary ovarian tumors resembling those of the pancreas. *Am J Surg Pathol* 2010; 34: 1514-20.
839. Baek JH, Lee JM, Kim SH, Kim SJ, Kim SH, Lee JY, Han JK, Choi BI. Small (<3 cm) solid pseudopapillary tumors of the pancreas at multiphasic multidetector CT. *Radiology* 2010; 257: 97-106.
840. Watanabe D, Miura K, Goto T, Nanjo H, Yamamoto Y, Ohnishi H. Solid pseudopapillary tumor of the pancreas with concomitant pancreas divisum. A case report. *JOP* 2010; 11: 45-8.
841. El-Bahrawy MA, Khorsandy S, Williamson R, Stamp G. Spindle cell solid pseudopapillary tumor of the pancreas: a newly described variant. *Pancreas* 2010; 39: 255-7 (letter).
842. Ban D, Shimada K, Sekine S, Sakamoto Y, Kosuge T, Kanai Y, Hiraoka N. Pancreatic ducts as an important route of tumor extension for acinar cell carcinoma of the pancreas. *Am J Surg Pathol* 2010; 34: 1025-36.
843. Fujii M, Sato H, Ogasawara T, Ando T, Tsujii S, Nagahori J, Komatsu Y, Matsuoka A. A case of liver metastasis of pancreatic acinar cell carcinoma treated with S-1 and intra-arterial CDDP combination therapy. *Gan To Kagaku Ryoho* 2010; 37: 1987-90 (in Japanese).
844. Trikudanathan G, Dasanu CA. Adenosquamous carcinoma of the pancreas: a distinct clinicopathologic entity. *South Med J* 2010; 103: 903-10.
845. Fitzmaurice C, Cornett DD, Spier BJ, Pfau P. Metastatic pancreatic small-cell carcinoma presenting as acute pancreatitis. *J Clin Oncol* 2010 Sep 13 [Epub ahead of print].
846. Fischer MA, Donati O, Heinrich S, Weber A, Hany TF, Soldini D, Alkadhi H, Marincek B, Scheffel H. Intraductal oncocytic papillary neoplasm of the pancreas: a radio-pathological case study. *JOP* 2010; 11: 49-54.
847. Jacob S, Rawat P, Mark RP. Serous microcystic adenoma (glycogen rich cystadenoma) of the pancreas. *Indian J Pathol Microbiol* 2010; 53: 106-8.
848. Stelow EB, Shaco-Levy R, Bao F, Garcia J, Klimstra DS. Pancreatic acinar cell carcinomas with prominent ductal differentiation: mixed acinar ductal carcinoma and mixed acinar endocrine ductal carcinoma. *Am J Surg Pathol* 2010; 34: 510-8.
849. Kobayashi S, Asakura T, Ohike N, Enomoto T, Sakurai J, Koizumi S, Watanabe T, Nakano H, Otsubo T. Mixed acinar-endocrine carcinoma of the pancreas with intraductal growth into the main pancreatic duct: Report of a case. *Surg Today* 2010; 40: 380-4.
850. Voong KR, Davison J, Pawlik TM, Uy MO, Hsu CC, Winter J, Hruban RH, Laheru D, Rudra S, Swartz MJ, Nathan H, Edil BH, Schulick R, Cameron JL, Wolfgang CL, Herman JM. Resected pancreatic adenosquamous carcinoma: clinicopathologic review and evaluation of adjuvant chemotherapy and radiation in 38 patients. *Hum Pathol* 2010; 41: 113-22.
851. Suzuki S, Kaji S, Koike N, Harada N, Hayashi T, Suzuki M, Hanyu F, Ban S. Pancreatic schwannoma: a case report and literature review with special reference to imaging features. *JOP* 2010; 11: 31-5.
852. Stojanovic MP, Radojkovic M, Jeremic LM, Zlatic AV, Stanojevic GZ, Jovanovic MA, Kostov MS, Katic VP. Malignant schwannoma of the pancreas involving transversal colon treated with en-bloc resection. *World J Gastroenterol* 2010; 16: 119-22.
853. Zhan HX, Zhang TP, Liu BN, Liao Q, Zhao YP. A systematic review of pancreatic lipoma: how come there are so few cases? *Pancreas* 2010; 39: 257-60 (letter).

854. Temizoz O, Genchellac H, Unlu E, Kantarci F, Umit H, Demir MK. Incidental pancreatic lipomas: computed tomography imaging findings with emphasis on diagnostic challenges. *Can Assoc Radiol J* 2010; 61: 156-61.
855. Altinel D, Basturk O, Sarmiento J, Martin D, Jacobs MJ, Kooby DA, Adsay NV. Lipomatous pseudohypertrophy of the pancreas: a clinicopathologically distinct entity. *Pancreas* 2010; 39: 392-7.
856. Ohata R, Okazaki T, Ishizaki Y, Fujimura J, Shimizu T, Lane GJ, Yamataka A, Kawasaki S. Pancreaticoduodenectomy for pancreatoblastoma: a case report and literature review. *Pediatr Surg Int* 2010; 26: 447-50.
857. Huang YL, Yang YL, Hsu WM, Lai HS, Lin KH, Jou ST, Lu MY, Chang HH, Lin DT. Pancreatoblastoma: two case reports from a medical center in Taiwan. *J Pediatr Hematol Oncol* 2010; 32: 243-5.
858. Dall'igna P, Cecchetto G, Bisogno G, Conte M, Chiesa PL, D'Angelo P, De Leonardis F, De Salvo G, Favini F, Ferrari A; TREP Group. Pancreatic tumors in children and adolescents: the Italian TREP project experience. *Pediatr Blood Cancer* 2010; 54: 675-80.
859. Espinal-Witter R, Servais EL, Klimstra DS, Lieberman MD, Yantiss RK. Localized intrapancreatic malignant mesothelioma: a rare entity that may be confused with other pancreatic neoplasms. *Virchows Arch* 2010; 456:455-61.
860. Zhang H, Jensen MH, Farnell MB, Smyrk TC, Zhang L. Primary leiomyosarcoma of the pancreas: study of 9 cases and review of literature. *Am J Surg Pathol* 2010; 34: 1849-56.
861. Bu X, Dai X. Primary mesenchymal chondrosarcoma of the pancreas. *Ann R Coll Surg Engl* 2010; 92: W10-2.
862. Pinto-Marques P, Martins C, Mendonça E, Castro H, Serra D. Pancreatic head mass of unusual etiology: multiple myeloma diagnosed by endoscopic ultrasound-guided fine needle aspiration. *Endoscopy* 2010; 42 Suppl 2: E263-4.
863. Daniel SV, Vani DH, Smith AM, Hill QA, Menon KV. Obstructive jaundice due to a pancreatic mass: a rare presentation of acute lymphoblastic leukaemia in an adult. *JOP* 2010; 11: 72-4.
864. Du XA, Zhao YP, Zhang TP, Liao QA, Dai MH, Liu ZW, Guo YC, Hu Y. Primary pancreatic lymphoma. A clinical quandary of diagnosis and treatment. *Pancreas* 2011; 40: 10-5.
865. Yoon WJ, Yoon YB, Kim YJ, Ryu JK, Kim YT. Primary pancreatic lymphoma in Korea – a single center experience. *J Korean Med Sci* 2010; 25: 536-40.
866. Rossi ED, Larghi A, Verna EC, Martini M, Galasso D, Carnuccio A, Larocca LM, Costamagna G, Fadda G. Endoscopic ultrasound-guided fine-needle aspiration with liquid-based cytologic preparation in the diagnosis of primary pancreatic lymphoma. *Pancreas* 2010; 39: 1299-1302.
867. Yun J, Kim SJ, Kim JA, Kong JH, Lee SH, Kim K, Ko YH, Kim WS. Clinical features and treatment outcomes of non-Hodgkin's lymphomas involving rare extranodal sites: a single-center experience. *Acta Haematol* 2010; 123: 48-54.
868. Aftandilian CC, Friedmann AM. Burkitt lymphoma with pancreatic involvement. *J Pediatr Hematol Oncol* 2010; 32: e338-40.
869. Konstantinidis IT, Dursun A, Zheng H, Wargo JA, Thayer SP, Fernandez-del Castillo C, Warshaw AL, Ferrone CR. Metastatic tumors in the pancreas in the modern era. *J Am Coll Surg* 2010; 211: 749-53.
870. Vagefi PA, Stangenberg L, Krings G, Forcione DG, Wargo JA. Ocular melanoma metastatic to the pancreas after a 28-year disease-free interval. *Surgery* 2010; 148: 151-4.

871. Sweeney AD, Fisher WE, Wu MF, Hilsenbeck SG, Brunnicardi FC. Value of pancreatic resection for cancer metastatic to the pancreas. *J Surg Res* 2010; 160: 268-76.
872. Masetti M, Zanini N, Martuzzi F, Fabbri C, Mastrangelo L, Landolfo G, Fornelli A, Burzi M, Vezzelli E, Jovine E. Analysis of prognostic factors in metastatic tumors of the pancreas: a single-center experience and review of the literature. *Pancreas* 2010; 39: 135-43.
873. Guan YS, Zou Q, He Q. Invading and long-lasting enormous pancreatic head tumor. *Pancreas* 2010; 39: 112-4 (letter).
874. Goh BK, Goh BK, Kesavan SM, Yap WM, Chung YF, Wong WK. Outcome after curative resection of large (≥ 10 cm) gastric gastrointestinal stromal tumors: how frequent is adjacent organ involvement and is concomitant distal pancreatectomy necessary? *J Gastrointest Surg* 2010; 14: 607-13.
875. Hirabayashi K, Fujihira T, Oyamada H, Serizawa A, Yamashita T, Tobita K, Imaizumi T, Kajiwara H, Nakamura N, Osamura RY. First case of primary phyllodes tumor of the pancreas: case report and findings of immunohistochemical and ultrastructural studies. *Virchows Arch* 2010; 456: 587-93.
876. Charalabopoulos A, Misiakos EP, Foukas P, Tsapralis D, Charalampopoulos A, Liakakos T, Macheras A. Localized peripancreatic plasma cell Castleman disease. *Am J Surg* 2010; 199: e51-3.
877. Nam SJ, Hwang HK, Kim H, Yu JS, Yoon DS, Chung JJ, Kim JH, Kim KW. Lymphoepithelial cysts in the pancreas: MRI of two cases with emphasis of diffusion-weighted imaging characteristics. *J Magn Reson Imaging* 2010; 32: 692-6.
878. Hutchinson CB, Canlas K, Evans JA, Obando JV, Waugh M. Endoscopic ultrasound-guided fine needle aspiration biopsy of the intrapancreatic accessory spleen: a report of 2 cases. *Acta Cytol* 2010; 54: 337-40.
879. Scudiere JR, Shi C, Hruban RH, Herman JM, Fishman EK, Schulick RD, Wolfgang CL, Makary MA, Thornton K, Montgomery E, Horton KM. Sclerosing mesenteritis involving the pancreas: a mimicker of pancreatic cancer. *Am J Surg Pathol* 2010; 34: 447-53.
880. Baker B, Salameh H, Daoud F. Idiopathic retroperitoneal fibrosis of the pancreas versus pancreatic carcinoma. *Ann R Coll Surg Engl* 2010; 92: W1-2.
881. Wijkström M, Bechara RI, Sarmiento JM. A rare nonmalignant mass of the pancreas: case report and review of pancreatic sarcoidosis. *Am Surg* 2010; 76: 79-84.
882. Modlin IM, Moss SF, Öberg K, Padbury R, Hicks RJ, Gustafsson BI, Wright NA, Kidd M. Gastrointestinal neuroendocrine (carcinoid) tumours: current diagnosis and management. *Med J Aust* 2010; 193: 46-52.
883. Zerbi A, Falconi M, Rindi G, Delle Fave G, Tomassetti P, Pasquali C, Capitanio V, Boninsegna L, Di Carlo V; AISP-Network Study Group. Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. *Am J Gastroenterol* 2010; 105: 1421-9.
884. Solorzano CC, Sosa JA, Lechner SC, Lew JI, Roman SA. Endocrine surgery: where are we today? A national survey of young endocrine surgeons. *Surgery* 2010; 147: 536-41.
885. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez Del Prado MP, Alonso Orduña V, Sevilla-García I, Villabona-Artero C, Beguiristain-Gómez A, Llanos-Muñoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jiménez-Fonseca P, Teulé A, Sastre-Valera J, Benavent-Viñuelas M, Monleon A, Salazar R. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol* 2010; 21: 1794-803.
886. Kuiper P, Verspaget HW, van Slooten HJ, Overbeek L, Biemond I, Lamers CB. Pathological incidence of duodenopancreatic neuroendocrine tumors in The Netherlands: A pathologisch anatomisch Landelijk Geautomatiseerd Archief Study. *Pancreas* 2010; 39: 1134-9.

887. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors. A review of nomenclature, grading, and staging systems. *Pancreas* 2010; 39: 707-12.
888. Long KB, Srivastava A, Hirsch MS, Hornick JL. PAX8 Expression in well-differentiated pancreatic endocrine tumors: correlation with clinicopathologic features and comparison with gastrointestinal and pulmonary carcinoid tumors. *Am J Surg Pathol* 2010; 34: 723-9.
889. Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin A – biological function and clinical utility in neuro endocrine tumor disease. *Ann Surg Oncol* 2010; 17: 2427-43.
890. Shah SA, Amarapurkar AD, Prabhu SR, Kumar V, Gangurde GK, Joshi RM. Splenic mass and isolated gastric varices: a rare presentation of a neuroendocrine tumor of the pancreas. *JOP* 2010; 11: 444-5.
891. Morimoto S, Morales A, Zambrano E, Fernandez-Mejia C. Sex steroids effects on the endocrine pancreas. *J Steroid Biochem Mol Biol* 2010; 122: 107-13.
892. Shi C, Siegelman SS, Kawamoto S, Wolfgang CL, Schulick RD, Maitra A, Hruban RH. Pancreatic duct stenosis secondary to small endocrine neoplasms: a manifestation of serotonin production? *Radiology* 2010; 257: 107-14.
893. Druce MR, Muthuppalaniappan VM, O'Leary B, Chew SL, Drake WM, Monson JP, Akker SA, Besser M, Sahdev A, Rockall A, Vyas S, Bhattacharya S, Matson M, Berney D, Reznek RH, Grossman AB. Diagnosis and localisation of insulinoma: the value of modern magnetic resonance imaging in conjunction with calcium stimulation catheterisation. *Eur J Endocrinol* 2010; 162: 971-8.
894. Janem W, Sultan I, Ajlouni F, Deebajeh R, Haddad H, Sughayer MA, Goussous RY. Malignant insulinoma in a child. *Pediatr Blood Cancer* 2010; 55: 1423-6.
895. Chandra P, Yarandi SS, Khazai N, Jacobs S, Umpierrez GE. Management of intractable hypoglycemia with Yttrium-90 radioembolization in a patient with malignant insulinoma. *Am J Med Sci* 2010; 340: 414-7.
896. Dejkhamron P, Unachak K, Thanarattanakorn P, Charoenkwan P, Tantiprabha W, Chotinaruemol S, Chaiwun B. Persistent hyperinsulinemic hypoglycemia of infancy associated with congenital neuroblastoma: a case report. *Med Assoc Thai* 2010; 93: 745-8.
897. McElroy MK, Lowy AM, Weidner N. Case report: focal nesidioblastosis ("nesidioblastoma") in an adult. *Hum Pathol* 2010; 41: 447-51.
898. Kuiper P, Biemond I, Masclee AA, Jansen JB, Verspaget HW, Lamers CB. Diagnostic efficacy of the secretin stimulation test for the Zollinger-Ellison syndrome: an intra-individual comparison using different dosages in patients and controls. *Pancreatology* 2010; 10: 14-8.
899. Wu PH, Pan CC, Huang ZL, Li W, Zhao M, Zhou ZW. Percutaneous radiofrequency ablation approach through the spleen: initial case report for pancreatic tail gastrinoma. *Chin J Cancer* 2010; 29: 836-41.
900. Do Cao C, Mekinian A, Ladsous M, Aubert S, D'Herbomez M, Pattou F, Bourdelle-Hego MF, Wémeau JL. Hypercalcitonemia revealing a somatostatinoma. *Ann Endocrinol (Paris)* 2010 Sep 1[Epub ahead of print].
901. Corleto VD. Somatostatin and the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes* 2010; 17: 63-8.
902. Zhang B, Xie QP, Gao SL, Fu YB, Wu YL. Pancreatic somatostatinoma with obscure inhibitory syndrome and mixed pathological pattern. *J Zhejiang Univ Sci B* 2010; 11: 22-6.

903. Almeida MQ, Stratakis CA. Solid tumors associated with multiple endocrine neoplasias. *Cancer Genet Cytogenet* 2010; 203: 30-6.
904. Serewko-Auret M, Mould AW, Loffler KA, Duncan R, Kay GF, Hayward NK. Alterations in gene expression in MEN1-associated insulinoma development. *Pancreas* 2010; 39: 1140-6.
905. Kimura N, Komuro K, Uchino S, Yagihashi S, Ishidate T, Ishizaka M. Multiple endocrine neoplasia type 1-associated cystic pancreatic endocrine neoplasia and multifocal cholesterol granulomas. *Pathol Int* 2010; 60: 321-5.
906. Squillaci S, Marchione R, Piccolomini M, Colombo F, Bucci F, Bruno M, Bisceglia M. Well-differentiated neuroendocrine carcinoma (malignant carcinoid) of the extrahepatic biliary tract: report of two cases and literature review. *APMIS* 2010; 118: 543-56.
907. Casadei R, Ricci C, Rega D, D'Ambra M, Pezzilli R, Tomassetti P, Campana D, Nori F, Minni F. Pancreatic endocrine tumors less than 4 cm in diameter: resect or enucleate? A single-center experience. *Pancreas* 2010; 39: 825-8.
908. Smith JK, Ng SC, Hill JS, Simons JP, Arous EJ, Shah SA, Tseng JF, McDade TP. Complications after pancreatectomy for neuroendocrine tumors: a national study. *J Surg Res* 2010; 163: 63-8.
909. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2010 Sep 7 [Epub ahead of print].
910. Iwasa S, Morizane C, Okusaka T, Ueno H, Ikeda M, Kondo S, Tanaka T, Nakachi K, Mitsunaga S, Kojima Y, Hagihara A, Hiraoka N. Cisplatin and etoposide as first-line chemotherapy for poorly differentiated neuroendocrine carcinoma of the hepatobiliary tract and pancreas. *Jpn J Clin Oncol* 2010; 40: 313-8.
911. Joseph S, Li G, Lindholm E, Zhou Y, Go VLW, Vinik AI, O'Dorisio TM, Mamikunian G, Woltering E. A prospective trial on the effect of body mass index and sex on plasma octreotide levels in patients undergoing long-term octreotide LAR therapy. *Pancreas* 2010; 39: 964-6.
912. Thapa R, Mallick D, Biswas B. Childhood Plasmodium falciparum malaria complicated by acute pancreatitis. *Trop Doct* 2010; 40: 184-5.
913. Asim S, Manjari L, Kenneth MS, Alexander CR, Christopher K, Khok-Yu H. Pancreatic abscess diagnosed by endoscopic ultrasound-guided fine needle aspiration. *J Pak Med Assoc* 2010; 60: 499-501.
914. Sahay SJ, Gonzalez HD, Luong TV, Rahman SH. Pancreatic actinomycosis as a cause of retroperitoneal fibrosis in a patient with chronic pancreatitis. Case report and literature review. *JOP* 2010; 11: 477-9.
915. Paganini CBL, Ferreira AB, Minanni CA, Lopes de Pontes FS, Ribeiro C, Silva RA, Pacheco AM, de Moricz A, De Campos T. Blastomycosis: a differential diagnosis of periampullary tumors. *Pancreas* 2010; 39: 1120-2 (letter).
916. Thomasset SC, Berry DP, Garcea G, Ong SL, Hall T, Rees Y, Sutton CD, Dennison AR. A simple, safe technique for the drainage of pancreatic pseudocysts. *ANZ J Surg* 2010; 80: 609-14.
917. Honda H, Miyatani H, Ikeya T, Yamanaka K, Ikeda M, Ushimaru S, Takamatsu T, Iwaki T, Sagihara N, Yoshida Y. Endoscopic ultrasound-guided transmural cyst drainage (EUS-CD) was effective in a case of pancreatic pseudocyst with obstructive jaundice and duodenal stenosis. *Nippon Shokakibyo Gakkai Zasshi* 2010; 107: 1497-504.
918. Fogue-Lafitte ME, Arambam R, Bara J. Proteases present in some pancreatic cyst fluids may affect mucin immunoassay by degrading antibodies and antigens. *Pancreas* 2010; 39: 1070-6.

919. Gaba RC, Mun SJ, Ryu RK, Lewandowski RJ, Martin JA, Salem R. A simple fluoroscopic approach to percutaneous transgastric cystgastrostomy with internalized drainage catheter for treatment of pancreatic pseudocysts: report of two cases. *Dig Dis Sci* 2010; 55: 523-8.
920. Trevino JM, Varadarajulu S. Endoscopic ultrasound-guided transjejunal drainage of pancreatic pseudocyst. *Pancreas* 2010; 39: 419-20 (letter).
921. Rossini CJ, Moriarty KP, Angelides AG. Hybrid notes: incisionless intragastric stapled cystgastrostomy of a pancreatic pseudocyst. *J Pediatr Surg* 2010; 45: 80-3.
922. Forgue-Lafitte ME, Arambam R, Bara J. Proteases present in some pancreatic cyst fluids may affect mucin immunoassay by degrading antibodies and antigens. *Pancreas* 2010; 39: 1070-6.
923. Lat A, Thompson GR 3rd, Rinaldi MG, Dorsey SA, Pennick G, Lewis JS 2nd. Micafungin concentrations from brain tissue and pancreatic pseudocyst fluid. *Antimicrob Agents Chemother* 2010; 54: 943-4.
924. Briem-Richter A, Grabhorn E, Wenke K, Ganschow R. Hemorrhagic necrotizing pancreatitis with a huge pseudocyst in a child with Crohn's disease. *Eur J Gastroenterol Hepatol* 2010; 22: 234-6.
925. Kibria R, Akram S, Ali SA. Successful endoscopic transpapillary management of intrahepatic pancreatic pseudocyst. *JOP* 2010; 11: 41-4.
926. Ritter JC, Johnston M, Caruana MF, Laws PE. Aorto-gastroduodenal bypass grafting for an inferior pancreaticoduodenal aneurysm and celiac trunk thrombosis. *Interact Cardiovasc Thorac Surg* 2010; 10: 125-7.
927. Dave B, Sharma A, Kwolek C, Demoya M, Wicky S, Kalva S. Percutaneous transcatheter arterial embolization of inferior pancreaticoduodenal artery aneurysms associated with celiac artery stenosis or occlusion. *Catheter Cardiovasc Interv* 2010; 75: 663-72.
928. Torii T, Sakurai M, Mikami C, Ono M, Hayashi Y, Katsuya M, Usui J. Survey of nutrient and food-group intake of cancer outpatients given chemotherapy. *Gan To Kagaku Ryoho* 2010; 37: 93-8 (in Japanese).
929. Tsai MT, Sun JT, Tsai KC, Lien WC. Isolated traumatic pancreatic rupture. *Am J Emerg Med* 2010; 28: 745.e3-4.
930. Rekhi S, Anderson SW, Rhea JT, Soto JA. Imaging of blunt pancreatic trauma. *Emerg Radiol* 2010; 17: 13-9.
931. Byard RW, Heath K. Mesenteric fibrosis – a histologic marker of previous blunt abdominal trauma in early childhood. *Int J Legal Med* 2010; 124: 71-3.
932. Patil DT, Yerian LM. Pancreas transplant: recent advances and spectrum of features in pancreas allograft pathology. *Adv Antra Pathol* 2010; 17: 202-8.
933. Sener A, Cooper M, Bartlett ST. Is there a role for pancreas transplantation in type 2 diabetes mellitus? *Transplantation* 2010; 90: 121-3.
934. Poommipanit N, Sampaio MS, Cho Y, Young B, Shah T, Pham PT, Wilkinson A, Danovitch G, Bunnapradist S. Pancreas after living donor kidney versus simultaneous pancreas-kidney transplant: an analysis of the organ procurement transplant network/united network of organ sharing database. *Transplantation* 2010; 89: 1496-503.
935. Rostambeigi N, Kudva YC, John S, Mailankody S, Pedersen RA, Dean PG, Prieto M, Cosio FG, Kremers WK, Walker RC, Abraham RS, Stegall MD. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. *Transplantation* 2010; 89: 1126-33.