REVIEW OF LITERATURE ON CLINICAL PANCREATOLOGY

Scientific literature made available in 2009

Selected and edited by

Åke Andrén-Sandberg & Omid Azodi

From the Department of Surgery, Karolinska Institutet at Karolinska University Hospital, Huddinge, S-141 86 Stockholm, Sweden

REVIEWER'S PREFACE (and SEARCH ALGORITM)

The scientific literature also in small medical subjects like pancreatology is today enormous – and it is not possible to keep updated unless making very strong and focused efforts. The present review is an attempt to make it easier for clinical pancreatologists to keep updated. From the beginning the consecutive quarterly reviews were an effort to make the reviewers updated, but hopefully it can be used also of others with the same interest, i.e. clinical pancreatology. However, it will still be a personal review, which means that the selection of presented articles have been up to the reviewers, and other authors should probably have made at least some other choises.

There must be made some limitations, otherwise a review in this form should not be possible to write due to lack of time and lack of brain capacity, and probably not possible to read either. Regarding the limitations, first of all almost all of the articles have been read in their full length, but the writing here is 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 pancreatology in 2009".

A second limitation is that most of the selections has been made through PubMed; a few other sources (like the journals "Pancreas", "Pancreatology" and "Journal of the Pancreas") have also been scrutinized, but then more occasional and not systematically. The MeSHs in PubMed have been *pancreas*, *pancreatic neoplasm*, *acute pancreatitis, chronic pancreatitis, pancreatic trauma* and *pancreatic pseudocysts.* This will lead to a lack of some articles that might be of interest, e.g. in pancreatic physiology, but the border has to be set somewhere.

Another limitation is that almost all articles dealing with purely transplantation and diabetes (and most of endocrine pankreas) issues have been dropped. Also, this is a clinical oriented review and the term *human* has been used in the search algorithm. Therefore almost all "preclinical" articles have been neglected; i.e. molecular biology, cell lines studies and whole animal studies are not included except exceptionally (when the authors could not resist the temptation). This is not because the preclinical issues are not interesting, but because they are so numerous, and because it is much more difficult to evaluate the importance of them. Some may seem to be of little importance today, but might be the first paper for a new paradigm – other may represent the reverse.

One more thing, this review is not written in English and not even in Swedish but in the best Swinglish the authors can present. Maybe some of the sentences and word make you smile a little, but remember than that our Swedish probably still is much better than your English …

The plan is to follow this quarter by a new review next quartetr and next quarter and (it is then the quarter when the review was made available through PubMed that counts, not the month it was actually published). So, welcome with comments – and if the comments fail to appear, the next quarters and year will have the same disposition as the present. Welcome back next quarter!

Åke Andrén-Sandberg and Omid Azodi

Department of Surgery ("Gastrocentrum Kirurgi")
Karolinska University Hospital at Huddinge
SE-141 86 Stockholm
Sweden

ake.andren-sandberg@karolinska.se and sayed-omid.sadrazodi@ki.se

ABBREVIATION

AAP	acute alcoholic
ABP	acute biliary pancreatitis
ACLAM	activated leucocyte cell adhesion molecule (synonym CD166)
ACP	alcoholic chronic pancreatitis
ACP	anaplastic carcinoma of the pancreas
ADAMTS	a disintegrin and metalloprotease with thrombospondin motifs
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9
ADC	apparent diffusion coefficient
ADIPOQ	adiponectin gene
ACP	alcoholic chronic pancreatitis
ADM	acinar-ductal metaplasia
AGA	American Gastroenterological Association
aICAM-1	anti-ICAM-1 monoclonal antibody
AIP	autoimmune chronic pancreatitis
AJCC	American Joint Committee on Cancer
AOS	antioxidant status
ALB	albumin
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
APACHE II	Acute Physiology and Chronic Health Evaluation II
APAP	acetaminophen
APC	activated protein C
APC-PCI	activated protein C-protein C inhibitor
AS	antisense
AST	aspartate aminotransferase
AUROC	area under the receiver operator characteristic
BD	biliary drainage
BD-IPMN	branch duct intraductal papillary mucinous neoplasms
BMI	body mass index
BOFS	Bernard Organ Failure Score
BPDI	blunt pancreatoduodenal injury
CA 19-9	carbohydrate antigen 19-9
CAPAP	carboxypeptidase B activation peptide
CapCel	capecitabine and celecoxib
CBDS	common bile duct stone
CCK	cholecystokinin
CDK-2	cyclin-dependent kinase 2
Ccr	creatinine clearance
CCRT	chemotherapy and radiation therapy
CEA	carcinoembryonic antigen
CEACAM	CEA-related cell adhesion molecules
CEUS	contrast-enhanced ultrasonography
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFR	case fatality rate
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
COX-2	cyclooxygenase-2
CPB/N	celiac plexus block/neurolysis
CPR	curved planar reformation

CRP	C-reactive protein
CRT	chemoradiotherapy
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTRC	chymotrypsin C
Cygb/STAP	cytoglobin/stellate cell activation-associated protein
2D	2-dimensional
3D	3-dimensional
DBP	double-bypass procedure
DC	dendritic cell
dCK	deoxycytidine kinase
DGE	delayed gastric emptying
DIGE	difference gel electrophoresis
DLK1	delta-like 1 homolog
DM	diabetes mellitus
DMBA	7,12-dimethylbenzanthracene
DP	distal pancreatectomy
DPP-4	dipeptidyl peptidase-4
DSS	disease-specific survival
DTA	diphtheria toxin gene A chain
DU	duodenal ulcer
DUPAN-2	Duke pancreatic monoclonal antigen type 2
DUVR	vitamin D-effective ultraviolet radiation
DWI	diffusion-weighted imaging
ECM	extracellular matrix
ED	endoscopic drainage
EG	elastography
EGD	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EG-US	transcutaneous ultrasonography elastography
ELF	elastic light scattering fingerprinting
EMS	self-expandable metallic stent
EMT	epithelial-mesenchymal transition
EORTC	European Organization for Research and Treatment of Cancer
ERCP	endoscopic retrograde cholangiopancreatography
ERP	endoscopic retrograde pancreatography
ES	embryonic stem cells
ESWL	extracorporeal shock wave lithotripsy
ETDP	endoscopic transgastric distal pancreatectomy
EUROPAC	The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer
EUS	endoscopic ultrasound
EUS-CP	endoscopic ultrasound-guided cholangiopancreatography
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
EUS-TCB	endoscopic ultrasound-guided trucut biopsy
FACS	fluorescence activated cell scanning
FAMMM	familial atypical multiple mole melanoma
FAP	familial adenomatous polyposis
FASTK	Fas-activated serine/threonine kinase
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxy glucose-positron emission tomography
FEC	fecal elastase-1 concentrations
FI	fluorescence intensity
FISH	fluorescence in situ hybridization

FMF AIP	focal mass-forming autoimmune pancreatitis
FNA	fine-needle aspiration
FP	focal pancreatitis
FPC	familial pancreatic cancer
FRAP	ferric reducing ability of plasma
5-FU	5-fluorouracil
FVL	factor V Leiden
GEL	granulocytic epithelial lesions
GEM	gemcitabine hydrochloride
GemLip	liposomal gemcitabine
GEP-NET	gastrointestinal and pancreatic neuroendocrine tumors
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIST	gastrointestinal stromal tumor
GLP-1	glucagon-like peptide-1
GSK-3beta	glycogen synthase kinase 3beta
GT	glutamyltransferase
GU	gastric ulcer
HCA	heterocyclic amines
HF	hemofiltration
HIF	hypoxia inducible factor
h-IAPP	hormone human islet amyloid polypeptide
hIPC	human islet-derived precursor cells
HLP	hyperlipoproteinemia
HMBG1	high-mobility group box 1
HOMA-IR	homeostasis model assessment of insulin resistance
HP	hereditary pancreatitis
hPSC	human pancreatic stellate cell
HRQOL	health-related quality of life
HSP27	heat shock protein 27
HT	hyperthermia
HuR	Hu antigen R
IAPP	amyloid polypeptide
IAT	intraportal islet autotransplantation
ICAM-1	intercellular adhesion molecule-1
IC-IPMC	invasive carcinoma originating in intraductal papillary mucinous neoplasm
ICP	idiopathic chronic pancreatitis
ICU	intensive care unit
IDCP	idiopathic duct-centric chronic pancreatitis
IFABP	intestinal fatty acid binding protein
IgG4	immunoglobulin G4
IGF-1R	insulin-like growth factor 1 receptor
IHC	immunohistochemistry
IL	interleukin
IL-10	interleukin-10
IL-13Ralpha2	interleukin-13 receptor alpha2
IMT	inflammatory myofibroblastic tumor
INGAP	islet neogeneis-associated protein
IPMC	intraductal papillary mucinous carcinoma
IPMN	intraductal papillary mucinous neoplasm
IPMN-Br	branch duct intraductal papillary mucinous neoplasm
IPN	infected pancreatic necrosis
IPT	inflammatory pseudotumor
IS	invasion score

ITNP	intrathecal narcotics pump
JCGAIP	Japanese clinical guidelines for autoimmune pancreatitis
KOC	K homology domain containing protein overexpresssed in cancer
L-asp	L-asparaginase
LCM	laser-capture microdissection
LDL	low-density lipoprotein
LEBS	low-coherence enhanced backscattering
LN	lymph node
LNM	lymph node metastasis
LNR	lymph node ratio
LP	laparoscopic distal pancreatectomy
LPC	liver perfusion chemotherapy
LPSP	lymphoplasmacytic sclerosing pancreatitis
MABP	mild acute biliary pancreatitis
MCN	mucinous cystic neoplasm
MDCT	multidetector computer tomography
M3DD	maximum 3-dimensional diameter
MD-IPMN	main duct pancreatic intraductal papillary-mucinous neoplasm
mDNA	mitochondrial DNA
MEN-1	multiple endocrine neoplasia type 1
MEN-2	multiple endocrine neoplasia syndrome type 2
mFOLFOX	5-fluorouracil (5-FU), folinic acid, and oxaliplatin
mFOLFOX.3	5-fluorouracil (5-FU), folinic acid, and irinotecan
MIBG	metaiodobenzylguanidine
MI-IPMC	minimally invasive intraductal papillary mucinous neoplasm
Mm-MAST	a score measuring alcohol addiction
MMP	matrix metalloproteinase
MMR	mismatch repair
Mnd-QD	manganese-doped quantum dots
MOF	multiple organ
MPD	main pancreatic duct
MPR	multiplanar reformation
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance image
mRNA	messenger RNA
MSI	microsatellite instability
MST	median survival time
MT-SP1	matriptase
MTT	3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NACRT	neoadjuvant chemoradiation therapy
NET	neuroendocrine tumors
NEUROD1	neurogenic differentiation 1
NEUROG3	neurogenin 3
NF-kappaB	nuclear factor-kappaB
NGF	nerve growth factor
NIR	near-infrared
NOF	non organ failure
NOM	nonoperative management
NOTES	natural orifice transluminal endoscopic surgery
NOx	excretion of nitric oxide
NP	necrotizing pancreatitis
NPM	nucleophosmin
NPV	negative predictive values
NSE	neuron-specific enolase

ODP	open distal pancreatectomy
OF	organ failure
25(OH)D	25-hydroxyvitamin D
OR	odds ratios
OS	overall survival
PAC	pancreatic adenocarcinoma
PAF	platelet-activating factor
PAI-1	plasminogen activator inhibitor type 1
PAM	prediction analysis for microarrays
PanIN	pancreatic intraepithelial neoplasia
PAP-1	pancreatitis-associated protein 1
PBP	plasminogen-binding protein
PC	pancreatic cancer
PCD	percutaneous catheter drainage
PCI	protein C inhibitor
PD	peritoneal dialysis
PD	pancreatoduodenectomy
PDA	pancreatic ductal adenocarcinomas
PDAC	pancreatic ductal adenocarcinoma
PDI	pancreatic ductal injury .
PDX1	pancreatic duodenal homeobox factor 1
PECA	pancreatic endocrine carcinomas
PEG	polyethylene glycols
PEN	pancreatic endocrine neoplasm
PET	pancreatic endocrine tumor
PET	positron emission tomography
PF	progression-free
PFC	pancreatic fluid collections
PG	pancreaticogastrostomy
PGF1-alpha	prostaglandin F1-alpha
P4H-beta	prolyl 4-hydroxylase-beta
PI	pancreatic injury
PJ	pancreaticojejunostomy
PJS	Peutz-Jeghers syndrome
pNET	pancreatic neuroendocrine tumors
p-NPM	phosphorylated nucleophosmin
POD	postoperative days
POPF	postoperative pancreatic fistula
POU3F4	POU class 3 homeobox 4
PP	pancreatic polypeptide
PPARG	peroxisome proliferator-activated receptor-gamma
PPF	pancreaticopleural fistula
PPH	postpancreatectomy hemorrhage
PPPD	pylorus-preserving pancreatoduodenectomy
PRRT	peptide receptor radionuclide therapy
PPV	positive predictive values
PR	progesterone receptor
PSC	pancreatic stellate cells
PSCA	prostate stem cell antigen
PTCH	membrane receptor patched
PTFE	polytetrafluoroethylene
PVR	portal vein reconstruction
QD	quantum dots
QLQ	quality of life
QoL	quality of life

QSR	quantitative systematic review
reg I	regenerating gene I
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RPF	retroperitoneal fibrosis
RPL10	ribosomal protein L10
RR	relative risk
RRG	renal rim grade
RT	radiotherapy
RT/CT	radiochemotherapy
RT-PCR	reverse transcription polymerase chain reaction
SAP	severe acute pancreatitis
SCA	serous cystadenoma
SCPT	solid and cystic pseudopapillary tumor
SDCT	single-detector CT
SEER	Surveillance, Epidemiology, and End Results
SHH	sonic hedgehog
SIR	standardised incidence ratios
SMA	serous microcystic adenoma
SMA	smooth muscle actin
SMO	smoothened receptor
SMPR	secretin-stimulated magnetic resonance pancreatography
SMR	standardised mortality ratio
SO	sphincter of Oddi
SOD	superoxide dismutase
SOF	single organ failure
SOR	summary odds ratio
S1P	sphingosine-1-phosphate
SPDP	spleen-preserving distal pancreatectomy
SPINK-1	serine protease inhibitor Kazal type I
SPN	solid-pseudopapillary neoplasms
SPT	solid pseudopapillary tumor
sRAGE	soluble form of the receptor for advanced glycation end products
SS	sense
SSA	somatostatin analogs
sst2	somatostatin receptor subtype 2
sTNFR	soluble tumor necrosis factor receptors
SUV	standardized uptake value
TAP	trypsinogen activation peptide
TB	tuberculosis
TBARS	thiobarbituric acid reactive substances
TC	total cholesterol
TGF-beta	transforming growth factor-beta
TIMP-1	tissue inhibitor of metalloproteinase-1
TK	tyrosine kinase
Treg	regulatory T cells
TRH	thyrotropin-releasing hormone
TRHR	thyrotropin-releasing hormone receptor
TrkA	tyrosine kinase receptor A
TSP-1	thrombospondin-1
TTP	time to progression
UFT	uracil-tegafur
uPA	urokinase-type plasminogen activator
uPAR	urokinase-type plasminogen activator receptor
UBR2	ubiquitin-protein ligase E3 component n-recognin 2

US	United States
UTDT	urinary trypsinogen-2 dipstick test
VESD	volume equivalent sphere diameter
VTE	venous thromboembolism
ZES	Zollinger-Ellison syndrome
WHO	World Health Organisation
XIAP	X-linked inhibitor of apoptosis protein

CONTENT

REVIEWER'S PREFACE (and SEARCH ALGORITM)

ABBREVIATIONS

PANCREATIC HISTORY
Early concepts
- Pancreatic anatomy
- Pancreatic physiology

Early thoughts on pancreatic disease
Reinier de Graaf
Acute pancreatitis
- Nicholaes Tulp
- A new interest in pancreatitis
- Reginald Fitz
- Two types of pancreatitis
- Nicholas Senn
- Pancreatitis patophysiology
- Opie's common channel hypothesis
- Alcoholic pancreatitis
- Biochemical diagnosis
- Classification of acute pancreatitis
- Attempts to treat acute pancreatitis
- Gallstone pancreatitis

John Beard
Pancreatic surgery
- Pancreatic cysts
- First pancreatic resections
- Enucleation
- Billroth, Codivilla and Halstedt
- Biliary-enteric anastomosis
- Managing the pancreatic remnant
- Kausch and Hirschel
- Whipple and Braunschweig
- Rockey and Priestly
- Pancreatic duct drainage in chronic pancreatitis and pancreatic cancer
- Pancreatic transplantation

Modern pancreatic history
- Howard Reber
- John Howard
- Katsusuke Satake

PANCREATIC DEVELOPMENT, EMBRYOLOGY and ANATOMY
Factors influencing development
- Regenerating gene I
- Transforming growth factor-beta (TGF-beta)
- Islet neogenesis-associated protein
- Connexins
- Diphtheria toxin gene A chain (DTA)
- Cell-surface markers
- Oxygen
- Thyrotropin-releasing hormone

Pancreatic anatomy and malformations

- Ectopic pancreas
- Circumportal annulare
- Pancreas annulare
- Polyspleni and short pancreas
- Double common bile duct
- Anomal pancreatic duct system
- Agenesia of the dorsal pancreatic neck, body and tail
- Fatty pancreas
- Spleno-pancreatic fusion

PANCREATIC PHYSIOLOGY

- Sphincter of Oddi
- Feeding
- Studies of pancreatic duct secretion
  - Cholecystokinin
- Pancreatic function in the elderly
- Ethanol metabolism
- IAPP
- Glucose metabolism
  - Diabetic overview
  - Incretin mimetics
  - Stem cell therapy

HISTOPATHOLOGY

- Transplanting pancreatic islets

ACUTE PANCREATITIS

- Overall results
  - Mortality
- Epidemiology and demography
  - An increased incidence
  - Risk factors in the US
  - Germany
  - India
- Etiologic factors and factors of importance for development of pancreatitis
  - Cytokines
  - Zinc and copper
  - Propofol
  - Genetic polymorphism
  - Oxidative stress
  - Hemoconcentration
  - Caboxypeptidase B
  - Obesity
  - Dyslipedemia
  - Dominant dorsal duct syndrome
- Classification and prediction of severity
  - Scoring systems
  - Single factors
- High- versus low-volume hospitals
  - Acute pancreatitis
  - Cholecystectomy
- Diagnostics in acute pancreatitis
  - Symptoms
  - Urinary trypsinogen-2
  - Dip-slide diagnosis

- Hyperamylasemia
- Hyperlipedemia
- d-Dimer
- CT
- MR
- Economical aspects

Differential diagnosis

Acute pancreatitis in children

- Epidemiology
- Acute pancreatitis in pediatric acute lymphoblastic leukemia

Specific injuries

- Pulmonary injury
- Osteonecrosis
- Abdominal aortic aneurysm following acute pancreatitis
- Colonic obstruction in acute pancreatitis
- Pancreatitis in anorexia nervosa

Subgroups of acute forms of pancreatitis

- Gallstone-induced pancreatitis
- Hypercalcemia-induced pancreatitis
- Alcohol-induced pancreatitis
- Post-ERCP-pancreatitis
- Ischemic pancreatitis
- Drug-induced pancreatitis
- Infective pancreatitis

Attempts to non-surgical treatment

- Enteral nutrition
- Plasmapheresis of triglycerides
- Intravenous protease inhibitors
- Dialysis as a treatment for acute pancreatitis
- Peritoneal lavage
- Probiotics
- Antibiotics

Necrosectomy

- Minimal invasive methods
- Intraparenchymal pancreatic air
- Intrahepatic fluid collections
- Endoscopic treatment
- Radiologic interventions

Quality of life after acute pancreatitis

Experimental

CHRONIC PANCREATITIS

Epidemiology and demography

- China
- India
- Risk of cancer

Genetics

- CFTR
- Chymotrypsin C
- Spain

Possible etiological factors

- Homocysteinemia
- Changes in neurohormones
- Amino acids

Diagnostics

- Symptoms
- Endocopic ultrasography (EUS)
- ERCP in children
- Breath tests

Association with liver disease
Alcohol-induced chronic pancreatitis
Groove pancreatitis
Pain
- Theories on investigations of pain in patients with chronic pancreatitis
- Types of pain

Medical pain treatment
- Pancreatic enzymes as treatment for pain
- Safety of pancreatic enzyme supplementation

Surgical interventions
- Outcome of pancreatoduodenectomy
- Pancreatogastrostomy
- Longitudinal pancreatodjejunostomy
- Islet transplantation

Other interventions agains pain
- Pancreatic duct stenting
- Plexus block
- Radiotherapy

Halofunginol as prevention of fibrosis
Pancreatopleural fistulae
Maldigestion and nutrition
- Vitamins
- Nutritional support
- Influence of colostrums

Diabetes in chronic pancreatitis
- Function in diabetes mellitus

Pancreas divisum
Pancreatic stellate cells
Pancreatic duct stones
Duodenal dystrophy
Cystic fibrosis

AUTOIMMUNE PANCREATITIS

Pathogenesis
- Association with Helicobacter pylori
- Association with eosinophilia

Definitions and differential diagnosis
- A new antibody

Possible etiological factors
- K-ras
- TGF-beta1

Extrapancreatic manifestations
Mikulicz disease
Sclerosing cholangitis
Retroperitoneal fibrosis
Diagnostics
- CT
- PET-CT for differential diagnosis
- Positrone emission tomography

Missdiagnosis
Concomittant cancer

Case reports

HEREDITARY PANCREATITIS
Case report

PANCREATIC CANCER
Classification of pancreatic tumors
Demography and epidemiology
- Statistics in theory
- Importance of race
- Sweden
- Danmark
- France
- Korea
- Arctic pancreatic cancer
- Pancreatic compared to peripancreatic cancers
- Death at home

Etiological factors
- Read meat and risk of cancer
- Smoking
- Alcohol and smoking
- Life-style factors
- Carbohydrate intake
- Fructose
- Citrus fruits
- Pollution
- Radon
- Vitamine D
- Tocopherols
- Nitrate in drinking water
- Perfluorooctanoate
- Psoriasis

Genetic aspects
- Screening
- Lynch syndrome

Molecular biology
- Methodology
- ACLAM
- Actinin-4
- ADAMTS
- Annexin A5
- Basement membrane proteins
- BCRA1
- B7 ligand family
- Ciliogenesis
- COX-2
- CTNNB1
- Cytokines
- Cytokine polymorphism
- Doxycyclins
- Epidermal growth factor receptor
- Epithelial-mesenchymal transition
- Fibrinogen
- Glycogen synthas kinase inhibitor
- Hedgehog pathway

- HSP27
- HuR
- IGF-1 receptor
- Integrines
- Interleukin-13 receptor
- K-ras
- Matriptase
- Mitochondrial DNA
- NF-kappaB
- Osteopontin
- p21/p27
- p53
- Pain and nerve growth factor
- PPARG
- Plasminogen activator
- REG4
- Rosiglitazone
- Somatostatin receptor subtype 2
- Sphingolipids
- Synuclein-gamma
- Tyrosine kinases
- Urokinase-type plasminogen activator
- Vitamin D

Proteomics
- Proteomics from lymph node metastases

Familial pancreatic cancer
Histologic precursors
Experimental pancreatic cancer
Early pancreatic cancer
Staging
Prognostic factors
Pancreatic cancer diagnosing and staging
- Algorithm
- Tumor markers
- Contrast-enhanced ultrasonography
- Endoscopic ultrasonography
- Endoscopic ultrasound-guided fine-needle aspiration biopsi
- Endoscopic ultrasound-guided trucut biopsy
- Computed tomography
- PET-CT
- Magnetic resonance imaging (MRI)
- Elastograph
- Metabolomics
- Optical markers
- Quantum dots

Differential diagnosis
- Bronchogenic carcinoma
- Hydatide cyst
- GIST
- Chronic pancreatitis
- Pseudotumor

Special symptoms and signs
- Hemosuccus pancreaticus
- Venous tromboembolism
- Obesity

- Diabetes in pancreatic cancer
- Coeliac axis stenosis

Preoperative biliary drainage
- Experimental

Pancreatic cancer cachexia
Effect of age on outcome
Surgical techniques
- Pancreatojejunostomy
- Bioabsorbable staple line-reinforcement
- Total pancreatectomy
- Portal vein reconstruction
- Arterial reconstruction at pancreatic resection
- Extended lymphadenectomy
- Cryosurgery

Postoperative complications
Surgical results
- Long-term survival

Body and tail tumors
Distal pancreatectomy
Laparoscopic distal pancreatectomy
- Spleen-preserving laparoscopically
- NOTES

Renal function at pancreatoduodenectomy
Glucose monitoring
- Peroperatively
- Glucos metabolism after pancreatectomy

Palliation
- Palliative stenting

Prediction of survival
Quality of life
Quality of care
- Organization

Chemotherapy
- Adjuvants and neoadjuvants
- Palliative cytotoxic treatment
- Stem cell transplantation
- Betulin
- Curcumin
- Aloe
- Ginseng

MORE UNUSUAL TUMORS OF THE PANCREAS

Anaplastic carcinoma of the pancreas
Cystic pancreatic tumors
Intraductal papillary mucinous neoplasm (IPMN)
- Growth rate
- Ways of detection
- Risk of cancer
- Molecular biology
- Imaging
- Differential diagnoses
- Extrapancreatic tumors
- Predictive factors
- In immune suppressed patients
- Frozen section at operation

Hemodialysis
Serous cystadenomas
Serous microcystic adenoma
Mucinous adenoma
Solid and pseudopapillary tumor (Frantz's tumor)
Diagnosis
Differential diagnosis
Solid and cystic pseudopapillary tumors
Intraductal tubular carcinoma
Adenosquamous carcinoma
Pancreatic lymphoma
Small cell carcinoma of the pancreas
Non pancreatic periampullary tumors
Papilla of Vater tumors
Duodenal tumors
Local excision
Metastases to pancreas
Renal cell carcinoma
Colorectal carcinoma
Bronchial carcinoma
Diffuse retroperitoneal cystic abdominal lymphangiomatosis
Merkel cell carcinoma
Pancreatic tuberculosis

PANCREATIC PSEUDOCYSTS and ANEURYSMS
Pancreatic pseudocysts
Diagnostics
Case report
Hemosuccus pancreaticus
Pancreatic aneurysm

PANCREATIC TRAUMA

ENDOCRINE PANCREATIC TUMORS
History
Genetics
Familial endocrinopathias
Multiple endocrine neoplasia
Diagnostics
Somatostatinoma
VIPoma
Zollinger-Ellison syndrome
Insulinomas
Non-functioning tumor
Tumors of the papilla of Vater
Surgery
Medical treatment
Cytotoxic treatment
Metastatic endocrine cancers
Panniculitis
Overall survival
Quality of life

REFERENCES

ABBREVIATION

AAP	acute alcoholic
ABP	acute biliary pancreatitis
ACLAM	activated leucocyte cell adhesion molecule (synonym CD166)
ACP	alcoholic chronic pancreatitis
ACP	anaplastic carcinoma of the pancreas
ADAMTS	a disintegrin and metalloprotease with thrombospondin motifs
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9
ADC	apparent diffusion coefficient
ADIPOQ	adiponectin gene
ACP	alcoholic chronic pancreatitis
ADM	acinar-ductal metaplasia
AGA	American Gastroenterological Association
aICAM-1	anti-ICAM-1 monoclonal antibody
AIP	autoimmune chronic pancreatitis
AJCC	American Joint Committee on Cancer
AOS	antioxidant status
ALB	albumin
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
APACHE II	Acute Physiology and Chronic Health Evaluation II
APAP	acetaminophen
APC	activated protein C
APC-PCI	activated protein C-protein C inhibitor
AS	antisense
AST	aspartate aminotransferase
AUROC	area under the receiver operator characteristic
BD	biliary drainage
BD-IPMN	branch duct intraductal papillary mucinous neoplasms
BMI	body mass index
BOFS	Bernard Organ Failure Score
BPDI	blunt pancreatoduodenal injury
CA 19-9	carbohydrate antigen 19-9
CAPAP	carboxypeptidase B activation peptide
CapCel	capecitabine and celecoxib
CBDS	common bile duct stone
CCK	cholecystokinin
CDK-2	cyclin-dependent kinase 2
Ccr	creatinine clearance
CCRT	chemotherapy and radiation therapy
CEA	carcinoembryonic antigen
CEACAM	CEA-related cell adhesion molecules
CEUS	contrast-enhanced ultrasonography
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFR	case fatality rate
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
COX-2	cyclooxygenase-2
CPB/N	celiac plexus block/neurolysis
CPR	curved planar reformation

CRP	C-reactive protein
CRT	chemoradiotherapy
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTRC	chymotrypsin C
Cygb/STAP	cytoglobin/stellate cell activation-associated protein
2D	2-dimensional
3D	3-dimensional
DBP	double-bypass procedure
DC	dendritic cell
dCK	deoxycytidine kinase
DGE	delayed gastric emptying
DIGE	difference gel electrophoresis
DLK1	delta-like 1 homolog
DM	diabetes mellitus
DMBA	7,12-dimethylbenzanthracene
DP	distal pancreatectomy
DPP-4	dipeptidyl peptidase-4
DSS	disease-specific survival
DTA	diphtheria toxin gene A chain
DU	duodenal ulcer
DUPAN-2	Duke pancreatic monoclonal antigen type 2
DUVR	vitamin D-effective ultraviolet radiation
DWI	diffusion-weighted imaging
ECM	extracellular matrix
ED	endoscopic drainage
EG	elastography
EGD	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EG-US	transcutaneous ultrasonography elastography
ELF	elastic light scattering fingerprinting
EMS	self-expandable metallic stent
EMT	epithelial-mesenchymal transition
EORTC	European Organization for Research and Treatment of Cancer
ERCP	endoscopic retrograde cholangiopancreatography
ERP	endoscopic retrograde pancreatography
ES	embryonic stem cells
ESWL	extracorporeal shock wave lithotripsy
ETDP	endoscopic transgastric distal pancreatectomy
EUROPAC	The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer
EUS	endoscopic ultrasound
EUS-CP	endoscopic ultrasound-guided cholangiopancreatography
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
EUS-TCB	endoscopic ultrasound-guided trucut biopsy
FACS	fluorescence activated cell scanning
FAMMM	familial atypical multiple mole melanoma
FAP	familial adenomatous polyposis
FASTK	Fas-activated serine/threonine kinase
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxy glucose-positron emission tomography
FEC	fecal elastase-1 concentrations
FI	fluorescence intensity
FISH	fluorescence in situ hybridization

FMF AIP	focal mass-forming autoimmune pancreatitis
FNA	fine-needle aspiration
FP	focal pancreatitis
FPC	familial pancreatic cancer
FRAP	ferric reducing ability of plasma
5-FU	5-fluorouracil
FVL	factor V Leiden
GEL	granulocytic epithelial lesions
GEM	gemcitabine hydrochloride
GemLip	liposomal gemcitabine
GEP-NET	gastrointestinal and pancreatic neuroendocrine tumors
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIST	gastrointestinal stromal tumor
GLP-1	glucagon-like peptide-1
GSK-3beta	glycogen synthase kinase 3beta
GT	glutamyltransferase
GU	gastric ulcer
HCA	heterocyclic amines
HF	hemofiltration
HIF	hypoxia inducible factor
h-IAPP	hormone human islet amyloid polypeptide
hIPC	human islet-derived precursor cells
HLP	hyperlipoproteinemia
HMBG1	high-mobility group box 1
HOMA-IR	homeostasis model assessment of insulin resistance
HP	hereditary pancreatitis
hPSC	human pancreatic stellate cell
HRQOL	health-related quality of life
HSP27	heat shock protein 27
HT	hyperthermia
HuR	Hu antigen R
IAPP	amyloid polypeptide
IAT	intraportal islet autotransplantation
ICAM-1	intercellular adhesion molecule-1
IC-IPMC	invasive carcinoma originating in intraductal papillary mucinous neoplasm
ICP	idiopathic chronic pancreatitis
ICU	intensive care unit
IDCP	idiopathic duct-centric chronic pancreatitis
IFABP	intestinal fatty acid binding protein
IgG4	immunoglobulin G4
IGF-1R	insulin-like growth factor 1 receptor
IHC	immunohistochemistry
IL	interleukin
IL-10	interleukin-10
IL-13Ralpha2	interleukin-13 receptor alpha2
IMT	inflammatory myofibroblastic tumor
INGAP	islet neogeneis-associated protein
IPMC	intraductal papillary mucinous carcinoma
IPMN	intraductal papillary mucinous neoplasm
IPMN-Br	branch duct intraductal papillary mucinous neoplasm
IPN	infected pancreatic necrosis
IPT	inflammatory pseudotumor
IS	invasion score

ITNP	intrathecal narcotics pump
JCGAIP	Japanese clinical guidelines for autoimmune pancreatitis
KOC	K homology domain containing protein overexpresssed in cancer
L-asp	L-asparaginase
LCM	laser-capture microdissection
LDL	low-density lipoprotein
LEBS	low-coherence enhanced backscattering
LN	lymph node
LNM	lymph node metastasis
LNR	lymph node ratio
LP	laparoscopic distal pancreatectomy
LPC	liver perfusion chemotherapy
LPSP	lymphoplasmacytic sclerosing pancreatitis
MABP	mild acute biliary pancreatitis
MCN	mucinous cystic neoplasm
MDCT	multidetector computer tomography
M3DD	maximum 3-dimensional diameter
MD-IPMN	main duct pancreatic intraductal papillary-mucinous neoplasm
mDNA	mitochondrial DNA
MEN-1	multiple endocrine neoplasia type 1
MEN-2	multiple endocrine neoplasia syndrome type 2
mFOLFOX	5-fluorouracil (5-FU), folinic acid, and oxaliplatin
mFOLFOX.3	5-fluorouracil (5-FU), folinic acid, and irinotecan
MIBG	metaiodobenzylguanidine
MI-IPMC	minimally invasive intraductal papillary mucinous neoplasm
Mm-MAST	a score measuring alcohol addiction
MMP	matrix metalloproteinase
MMR	mismatch repair
Mnd-QD	manganese-doped quantum dots
MOF	multiple organ
MPD	main pancreatic duct
MPR	multiplanar reformation
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance image
mRNA	messenger RNA
MSI	microsatellite instability
MST	median survival time
MT-SP1	matriptase
MTT	3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NACRT	neoadjuvant chemoradiation therapy
NET	neuroendocrine tumors
NEUROD1	neurogenic differentiation 1
NEUROG3	neurogenin 3
NF-kappaB	nuclear factor-kappaB
NGF	nerve growth factor
NIR	near-infrared
NOF	non organ failure
NOM	nonoperative management
NOTES	natural orifice transluminal endoscopic surgery
NOx	excretion of nitric oxide
NP	necrotizing pancreatitis
NPM	nucleophosmin
NPV	negative predictive values
NSE	neuron-specific enolase

ODP	open distal pancreatectomy
OF	organ failure
25(OH)D	25-hydroxyvitamin D
OR	odds ratios
OS	overall survival
PAC	pancreatic adenocarcinoma
PAF	platelet-activating factor
PAI-1	plasminogen activator inhibitor type 1
PAM	prediction analysis for microarrays
PanIN	pancreatic intraepithelial neoplasia
PAP-1	pancreatitis-associated protein 1
PBP	plasminogen-binding protein
PC	pancreatic cancer
PCD	percutaneous catheter drainage
PCI	protein C inhibitor
PD	peritoneal dialysis
PD	pancreatoduodenectomy
PDA	pancreatic ductal adenocarcinomas
PDAC	pancreatic ductal adenocarcinoma
PDI	pancreatic ductal injury .
PDX1	pancreatic duodenal homeobox factor 1
PECA	pancreatic endocrine carcinomas
PEG	polyethylene glycols
PEN	pancreatic endocrine neoplasm
PET	pancreatic endocrine tumor
PET	positron emission tomography
PF	progression-free
PFC	pancreatic fluid collections
PG	pancreaticogastrostomy
PGF1-alpha	prostaglandin F1-alpha
P4H-beta	prolyl 4-hydroxylase-beta
PI	pancreatic injury
PJ	pancreaticojejunostomy
PJS	Peutz-Jeghers syndrome
pNET	pancreatic neuroendocrine tumors
p-NPM	phosphorylated nucleophosmin
POD	postoperative days
POPF	postoperative pancreatic fistula
POU3F4	POU class 3 homeobox 4
PP	pancreatic polypeptide
PPARG	peroxisome proliferator-activated receptor-gamma
PPF	pancreaticopleural fistula
PPH	postpancreatectomy hemorrhage
PPPD	pylorus-preserving pancreatoduodenectomy
PRRT	peptide receptor radionuclide therapy
PPV	positive predictive values
PR	progesterone receptor
PSC	pancreatic stellate cells
PSCA	prostate stem cell antigen
PTCH	membrane receptor patched
PTFE	polytetrafluoroethylene
PVR	portal vein reconstruction
QD	quantum dots
QLQ	quality of life
QoL	quality of life

QSR	quantitative systematic review
reg I	regenerating gene I
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RPF	retroperitoneal fibrosis
RPL10	ribosomal protein L10
RR	relative risk
RRG	renal rim grade
RT	radiotherapy
RT/CT	radiochemotherapy
RT-PCR	reverse transcription polymerase chain reaction
SAP	severe acute pancreatitis
SCA	serous cystadenoma
SCPT	solid and cystic pseudopapillary tumor
SDCT	single-detector CT
SEER	Surveillance, Epidemiology, and End Results
SHH	sonic hedgehog
SIR	standardised incidence ratios
SMA	serous microcystic adenoma
SMA	smooth muscle actin
SMO	smoothened receptor
SMPR	secretin-stimulated magnetic resonance pancreatography
SMR	standardised mortality ratio
SO	sphincter of Oddi
SOD	superoxide dismutase
SOF	single organ failure
SOR	summary odds ratio
S1P	sphingosine-1-phosphate
SPDP	spleen-preserving distal pancreatectomy
SPINK-1	serine protease inhibitor Kazal type I
SPN	solid-pseudopapillary neoplasms
SPT	solid pseudopapillary tumor
sRAGE	soluble form of the receptor for advanced glycation end products
SS	sense
SSA	somatostatin analogs
sst2	somatostatin receptor subtype 2
sTNFR	soluble tumor necrosis factor receptors
SUV	standardized uptake value
TAP	trypsinogen activation peptide
TB	tuberculosis
TBARS	thiobarbituric acid reactive substances
TC	total cholesterol
TGF-beta	transforming growth factor-beta
TIMP-1	tissue inhibitor of metalloproteinase-1
TK	tyrosine kinase
Treg	regulatory T cells
TRH	thyrotropin-releasing hormone
TRHR	thyrotropin-releasing hormone receptor
TrkA	tyrosine kinase receptor A
TSP-1	thrombospondin-1
TTP	time to progression
UFT	uracil-tegafur
uPA	urokinase-type plasminogen activator
uPAR	urokinase-type plasminogen activator receptor
UBR2	ubiquitin-protein ligase E3 component n-recognin 2

US	United States
UTDT	urinary trypsinogen-2 dipstick test
VESD	volume equivalent sphere diameter
VTE	venous thromboembolism
ZES	Zollinger-Ellison syndrome
WHO	World Health Organisation
XIAP	X-linked inhibitor of apoptosis protein

PANCREATIC HISTORY

Early concepts

Pancreatic anatomy

The earliest observations on the pancreas were probably made by rabbis in the Babylonian Talmud who refer to a "finger of the liver" [001]. The initial anatomical descriptions of the pancreas are generally considered to have originated from the Alexandrians Herophilus, Erasistratos, and Eudemus in the third century BC [002, 003]. Although Galen provided a modest anatomical description, neither he, Hippocrates, Erasistratus, nor Herophilus were able to identify any relationship to disease. These ancient quasi anatomophysiologists regarded the pancreas as unusual, given that it had no cartilage or bone. This observation led Ruphos of Ephesus (c. 100 BC) to name the organ "pancreas" (Greek pan: all, + kreas: flesh or meat) [004, 005].

Andreas Vesalius (1513-1564) referred to the pancreas in the fifth book of his opus (De humani corporis fabrica) as a "glandulous organ or kannelly body of substance growing in the neather pannicle of the caule (omentum)" and postulated that the pancreas exerts a protective effect on the stomach by serving as a cushion (Schutzorgan) on which it rested [006].

In 1642, in an anatomical dissection of an executed criminal, Johann Wirsüng (1589-1643) described the main pancreatic duct, but neither he nor his contemporaries could decipher the function of the gland [007]. Giovanni Domenico Santorini (1681-1737) is credited with the discovery of the accessory pancreatic duct, although several other contemporary anatomists also reported on the existence of the accessory duct [008].

In 1720, Abraham Vater (1684-1751) presented his description of the duodenal ampulla [008], whereas Ruggero Oddi, as a fourth year medical student in 1887, demonstrated the existence of the sphincter, which bears his name [009]. The dubious history of this sphincter is recapitulated in Oddi's precipitous fall from scientific grace and his ignominious demise as a member of the French Foreign legion in an unknown grave in Tunisia [010].

Pancreatic physiology

Despite knowledge of the existence of the pancreas, there was little effort to investigate the physiological role of the gland until the late 17th century when Franciscus de le Boe Sylvius (1614-1672) of Amsterdam proposed that digestion was a multistep process starting with fermentation by saliva in the mouth and the stomach, a second phase involving the pancreas, followed by the passage of chyle into lymphatics, the venous system, and eventually, the right side of the heart [011]. His pupil, Regnier de Graaf (1641-1673), ingeniously developed a method for the direct investigation of the nature of pancreatic juice by creating canine pancreatic fistulae through which he inserted feather quills into the pancreatic ductal orifices to obtain succus pancreaticus [012]. However, his investigations into the nature of the succus pancreaticus resulted in his erroneous conclusion that it was acidic in nature (he had sampled the pyloric antra of his piscine models) [010].

These innovative theories on digestion were subsequently modified by John Conrad Brunner (1653-1727) whose experiments in pancreatectomized dogs led him to propose that specialized duodenal glands (which are named after him) were the major source of digestive juice secretion and that the pancreas was not vital either for digestion or for life [002, 013]. In 1682, Peyer described the lymphatic nodules located in the walls of the ileum and proposed that both Brunner glands and his own "patches" were adjuncts to digestion, producing a

fortifying secretion for the pancreatic juice [014]. This reductionist viewpoint sadly hindered pancreatic investigation for years by concluding that the pancreas was a minor contributor to digestion and the gland languished while scientists probed the stomach and liver as the key agents of digestion [010].

Further elucidation of pancreatic physiology was provided by Willy Kuhne (1837-1900) of Germany, who identified trypsin and evaluated its role in the digestion of protein, and by Alexander Marcet [011] (1770-1822), who identified lipase in 1815. Claude Bernard (1813-1878) of Paris demonstrated that gastric digestion "is only a preparation act" and that pancreatic juice emulsified fatty foods by splitting them into glycerin and fatty acids [015]. In addition, he demonstrated the role of the pancreas in the conversion of starch into sugar and its solvent action on the "proteides that have not been cleaved in the stomach." Further work by Eberle in 1843 demonstrated that pancreatic juice emulsified fat, and a year later, Valentin demonstrated its activity on starch [011].

The concept of the regulation of pancreatic secretion was initially addressed by Ivan Pavlov (1849-1936) and his pupils who proposed a dominant role of the vagus nerve in the neural regulation of pancreatic secretion. In 1902, William Bayliss (1860-1924) and Ernest Starling (1866-1927) of University College, London, demonstrated that this phenomenon was in fact not only a neural reflex but also the effect of a chemical messenger, which led them to introduce the word "hormone" (derived from the Greek hormonos: I arouse to excitement) and name the putative agent "secretin" [016]. Further developments in this field included the discovery of cholecystokinin by A. C. Ivy (1893-1978) and E. Oldberg (1901-1986) [017] and the understanding that a number of chemical messengers influenced different aspects (protein and water, bicarbonate) of pancreatic secretion [010].

Early thoughts on pancreatic disease

Although Galen (130-201 AC) was aware of pancreatic problems [018] the pancreas remained in virtual obscurity as a seat of disease until the late 16th century when there was a renaissance in the study of the gland largely initiated by the experiments of Franciscus de la Boe Sylvius (1614-1672) and his protégé, Regnier de Graaf (1641-1673) [011]. This renewed interest led to the pancreas being blamed for a variety of maladies. In 1835, JJ Bigsby (1792-1881) published a review of the existing literature on the pancreas [019]. He noted that one of the earliest mentions of pancreatic disease was by Jean Fernel (1509-1558), who, in 1542, believed that the pancreas was the origin of intermittent fevers and melancholy. Nearly a century later, Nathanael Highmore (1613-1687) ascribed apoplexy, palsy, and hysteria to affliction of the pancreas. In a review of 45 patients with acute pancreatitis, Heinrich Claessen, as late as 1842, remarked that pancreatic disease was rare and that it was difficult to obtain information about this organ that was deep-seated, had limited relationships to other organs of the body, and was purely an organ of excretion [020]. Interest in pancreatic diseases also waned after Brunner's experiment on the survival of pancreatectomized dogs, which led him to postulate that the pancreas was not a vital organ [003].

Reinier de Graaf

In the late seventeenth century, traditions in anatomy and chemistry came together to ground new theoretical and experimental approaches to understanding the animal body. The researches of Dutch experimenters Reinier de Graaf and his mentor Franciscus Sylvius provide keen insight into the ways experiments were constructed, negotiated, and thought about by leading anatomists and physicians of the time. The objects and approaches de Graaf used in the laboratory – ligature, inflation, injection, tubes, vessels, tasting – were

derived from broadly Harveian anatomical and Helmontian chymical traditions. Experimental traditions and a comprehensive and materialistic chymical theory of acid-alkali interactions unified the artificial and the natural and allowed de Graaf to create and use hybrid animal-apparatus constructions as tools to collect and assay the key ingredients of digestion and disease [021].

Acute pancreatitis

The death of Alexander the Great (356-323 BC) at the age of 33 has been ascribed to acute necrotizing pancreatitis secondary to rich food and heavy alcohol consumption [022].

Among the various pancreatic disorders, the pace of scientific discovery in acute pancreatitis has been particularly slow. A clinical description of acute pancreatitis was first presented in 1652 by the Dutch anatomist Nicholas Tulp, and despite the nearly 350 years that have passed, there continue to be many unanswered questions. In the late 19th and early 20th century, Reginald Fitz, Nicholas Senn, Eugene Opie, and others made seminal contributions that continue to influence our present understanding of acute pancreatitis [023].

Nicholaes Tulp

The first clinical description of acute pancreatitis is believed to have been published in 1652 by the Dutch anatomist Nicholaes Tulp (1593-1674) [005, 024]. Tulp, who is also remembered for discovering the ileocecal valve, reported the case of a young man who succumbed to an illness characterized by incessant fevers and much distress. On autopsy, the pancreas was "swollen with dirty pus and filled with an excess of viscous mucus" [024]. He speculated that the pancreas was "the origin of protracted and complicated diseases, such as consumption of the spine, continuous fever, cancer, abscesses, growths, vomiting, restlessness, sleeplessness, and other most dangerous affections, which from this source, like Pandora's box, frequently originate to the detriment of the human race." Tulp was a well-known physician and anatomist in Amsterdam and the praelector (lecturer) in Anatomy of the Surgeon's Guild from 1628 to 1653. In addition to being immortalized as the central figure in the Rembrandt painting, "Lesson in anatomy," Tulp published a considerable amount of his anatomical observations under the title "Observationum Medicarum Libri Tres" [025]. He was the chief editor of the Amsterdam Pharmacopoeia, and provided the first systematic catalog of medications in the Netherlands. Indeed, he was held in such public esteem that he was elected Burgermaster of Amsterdam four times. After Tulp's description, Théophile Bonet (1629-1689) [026] and JG Griesel [027] also reported on cases where the pancreas was necrotic on autopsy. Nearly a century later, Morgagni, in 1761, reported a clinical syndrome of severe upper abdominal pain, vomiting, and collapse in a patient whose autopsy revealed that the "pancreas was enlarged and totally filled with knots, rather large, unequal and of the consistency of cartilage" [010, 028].

A new interest in pancreatitis

These early descriptions of pancreatic disease failed to discriminate between acute and chronic pancreatitis, presented little insight into the pathological features of the pancreas on autopsy, and were highly speculative with regard to causes and clinical symptoms of pancreatitis. Antoine Portal (1742-1832), who was professor of medicine at the Collège de France, described the various pathological manifestations of pancreatic disease such as edema, hemorrhage, necrosis, and gangrene [029], although he considered these manifestations as different disease entities. Portal also reported recurring acute pancreatitis presenting with repeated bouts of intense pain that led to the eventual death of the patient from gangrene of the pancreas. Augustin-Nicolas Gendrin (1796-1890) also made

observations on acute pancreatitis which were similar to those of Portal [030]. Interestingly, these early authors noted an association between swelling of the salivary glands and inflammation of the pancreas. Théodoric Lerminier (1770-1836) observed that there was an analogy between the state of the pancreas and the parotid in severe fevers [031] and S. Neumann (1819-1908) and JT Mondière both proposed that inflammation could rapidly spread from the salivary glands to the pancreas resulting in the death of the patient [010, 032]. It was only in 1899 that HF Harris of Boston was convincingly able to link mumps and pancreatitis [033].

The etiology of pancreatic inflammation was a matter of intense speculation. Some of the proposed causative factors included mercury, which was used to treat syphilis at that time [003, 034], gastritis and continuous vomiting (Claessen, 1842) [020], chronic hepatic disease (Portal, 1803) [029], excessive masturbation (A von Störck, 1799) [035], migration of a worm from the duodenum to the pancreatic duct (Shea [036] and Lieutaud [037]), perforated gastric ulcer causing penetration of the pancreas (Andral) [031] and compression of the bile duct leading to pancreatitis with jaundice (Crampton, 1818) [038].

Karl von Rokitansky (1804-1878), chair of pathology at the Wiener Allgemeines Krankenhaus, was the first in 1842 to recognize acute hemorrhagic pancreatitis [039] followed by Theodor Albrecht Edwin Klebs (1834-1913) of Berne, who, in 1870, noted that hemorrhagic inflammation of the gland resulted in "purulent peripancreatitis with partial sequestration of the gland" [040]. TS Cullen (1867-1948) of Edinburgh described periumbilical discoloration in a patient with ectopic pregnancy, and this later came to be recognized as a sign of severe acute pancreatitis [041], whereas G Gray-Turner (1877-1951) of London, in 1920, reported flank discoloration associated with hemorrhagic pancreatitis [042].

In 1856, the great French physiologist Claude Bernard (1813-1878) demonstrated the capacity of pancreatic secretions to digest proteins, carbohydrate and fat. Bernard initially demonstrated fat necrosis in dogs in 1856 but failed to elucidate on his finding. He was followed by Julius Klob, an assistant of Rokitansky, who identified fat necrosis in humans in 1860. In 1882, F Balser described the process of fat necrosis in more detail but felt that this was a separate event from pancreatic inflammation. W Dettner, who, in 1894, proposed a pancreatic ferment as the cause, and H Chiari (1851-1916), who considered it to be due to pancreatic degeneration (1896), contested this. Further controversy was excited by Reginald Fitz (1843-1913), who thought the origin was bacterial infection and HD Rolleston who proposed it to be a solar plexus-related event. Robert Langerhans postulated that it was pancreatic ferment that resulted in necrosis of fat tissue, and Simon Flexner, in 1897, suggested that this ferment was lipase [010].

Reginald Fitz

In a seminal article published in 1889, Reginald Huber Fitz (1843-1913) of Boston presented the first systematic analyses of acute pancreatitis [032]. Fitz was born in Chelsea, Massachusets, and entered Harvard College in 1858 but left in his junior year to work in a copper mine [043]. He returned in 1862 to complete BA and MD degrees and then proceeded to Europe, where he acquired a unique blend of training in both clinical medicine and pathology under the guidance of such illustrious scientists as Rokitansky, Skoda, and Billroth. Fitz also worked in the laboratory of Rudolf Virchow (1821-1902), where he became an expert in microscopy and also brought to the United States Virchow's teaching that disease is an expression of aberration in normal cellular function. Having returned to Massachusetts, as an instructor in Pathology and later as Shattuck Professor of Pathologic Anatomy, he pioneered integration of clinical information with pathologic findings, and his perspicacity led to significant advances in surgical pathology including characterization of

acute appendicitis, intestinal obstruction, complications of Meckel diverticulum, and acute pancreatitis [010].

In 1889, at the New York Pathological Society's Middleton-Goldsmith lecture, Fitz presented his article entitled "Acute pancreatitis: a consideration of hemorrhage, hemorrhagic, suppurative, and gangrenous pancreatitis, and of disseminated fat necrosis" in which he systematically reviewed the clinical symptoms in 53 cases of pathologically documented acute pancreatitis [043]. In addition, he detailed the various hemorrhagic, suppurative, and gangrenous changes in acute pancreatitis and their pathological differentiation. He further commented on various etiologies such as gall stones, alcohol, perforating gastric ulcer, and trauma. Quite remarkably, Fitz also described pancreatic abscess, splenic vein thrombosis, and a likely pseudocyst of the pancreas as associated complications of acute pancreatitis. In this paper, Fitz also proposed a relationship between pancreatic hemorrhage and pancreatitis and a causal link between disseminated fat necrosis and acute pancreatitis [010].

By his systematic analysis of the various facets of acute pancreatitis, Fitz laid the foundation for antemortem diagnosis of this disease and greatly facilitated subsequent pancreatic research at the turn of the 20th century. Interestingly, Fitz initially advocated a conservative approach to the surgical management of patients with acute pancreatitis, noting that "an operation… in the early stages of this disease, is extremely hazardous" [044]. However, his recommendation later changed to early laparotomy as performed for other causes of acute abdomen [010].

Two types of pancreatitis

Despite the accumulating knowledge on pancreatitis, it was not until the middle of the 20th century that an understanding of the differences between acute and chronic pancreatitis was appreciated. However, there were multiple descriptions of pancreatic concretions in the 18th and 19th centuries. In 1678, de Graaf recounted previous reports of pancreatic stones by his contemporaries. After this, there were also numerous reports of pancreatic lithiasis at the time of autopsy by various authors including Bonet, Morgagni, and Johann Friedrich Meckel (1724-1774) [010]. In 1799, Matthew Baillie (1761-1823) of London published plates that clearly depicted pancreatic ductal concretions, ductal dilatation, and changes of chronic pancreatitis [045]. At the turn of the 19th century, Sir Arthur Mayo Robson (1853-1933) of Leeds presumed the etiology to be of bacterial infection; however, the distinction among acute, subacute, and chronic was still controversial [046, 047]. In 1946, Comfort [048], at the Mayo Clinic, provided a significant analysis of the clinical entity of chronic pancreatitis and, in so doing, produced the seminal manuscript on the subject that has, for 50 years, remained the critical commentary on the disease.

Nicholas Senn

One of the contemporaries of Reginald Fitz who contributed extensively to the advancement of our knowledge of the pancreas was Nicholas Senn (1844-1908), a surgeon who was born in Sweden but later moved to the United States and attended the Chicago Medical School [005]. He initially worked at the Cook County Hospital in Chicago and Milwaukee (Wisconsin) Hospital before proceeding to Munich for further training in surgery before finally returning to Rush Medical College as professor of surgery [010]. In 1886, Senn presented an extensive account of his surgical experiments on the pancreas at the meeting of the American Surgical Association as an article entitled "Surgery of the pancreas, as based upon experiments and clinical researches" [005, 049]. Starting with a review of the available surgical literature on the pancreas, Senn noted that the only operations available were either excision of retention cysts or formation of external pancreatic fistulas to drain such cysts [049]. He detailed a

series of animal experiments, of which one was transection of the pancreas followed by suturing to prevent hemorrhage. In this experiment, Senn concluded that the contiguous portion of the pancreas continued to secrete digestive juices and that extravasation of the pancreatic juice from the distal end of the gland into peritoneum did not have adverse consequences. He also disproved the prevailing notion of dead pancreatic tissue being a highly putrescible substance leading to infection by crushing a segment of the pancreatic glands of two cats under aseptic conditions. He concluded that the affected part of the gland is absorbed and replaced by connective tissue while the rest of the gland functions normally. Presciently, he also noted that if the outlet of the pancreas is affected, it leads to ductal obstruction from scarring and destruction of the gland [010].

His other experiments dealt with partial and total pancreatectomy, effects of the introduction of pancreatic juice into the peritoneal cavity, and the circulation, pancreatic fistulae, and gangrene of the pancreas. His observations on total pancreatectomy led him to caution against this operation because it could lead to "damage or necrosis of the duodenum." Senn recommended operative debridement of the gangrenous pancreas extrapolating case reports, which noted spontaneous recovery from gangrene of the pancreas by sloughing of the gland through the duodenum. Indeed, his experiments laid the foundation for future experimental work in pancreatic diseases, provided guiding principles for pancreatic surgery, and led him to being recognized as the "father of experimental pancreatology" [005].

Pancreatitis patophysiology

In 1896, Hans Chiari invoked a role for pancreatic enzymes in the pathogenesis of pancreatic necrosis and proposed a theory of tryptic autodigestion initiated by activation by bile as initially proposed by Claude Bernard or alternatively by enterokinase as had been suggested by Nicholas Petrovich Shepovalnikov in 1889 [050]. Gerhard Katsch (1887-1961), in 1939, expanded this concept based on Heidenhein's original 1875 recognition of the inactive forms of enzymes in pancreatic cells. He described the phenomenon of Fermentengleisung (derailment of enzymes) whereby circulating activated pancreatic enzymes resulted in damage to the lungs, kidneys, and capillaries. Similar explanations for hypocalcemia, fat necrosis, capillary permeability, pulmonary surfactant damage, and myocardial depression were considered by a variety of investigators between 1944 and 1970. None has proved to be more persuasive than the role of superimposed infection that Sir Berkeley Moynihan (1856-1936) had emphasized as early as 1925 [051].

Opie’s common channel hypothesis

It was only in the late 19th and the first part of the 20th century that the link between gallstones and pancreatitis was explored. Körte [052] and Oser [053] noted an association between diseases of the bile passages, especially cholelithiasis, and lesions of the pancreas and felt that inflammation can extend from the bile duct to the pancreas. Lancereaux [054] reported that a gallstone lodged in the common bile duct may occlude the pancreatic duct and produce conditions favorable to the penetration of microorganisms into the pancreas.

In 1901, Eugene L. Opie (1873-1971), a pathologist at Johns Hopkins Hospital, proposed the "common channel hypothesis" based on his observations at autopsy of cases of acute hemorrhagic pancreatitis [055-057]. In one case, he noticed a 7-mm stone in the distal common bile duct, which was dilated without associated dilatation of the pancreatic duct. He opined that the concretion created a common channel between the bile and pancreatic ducts resulting in reflux of bile into the pancreatic duct. To substantiate his hypothesis, he performed various animal experiments where he infused bile into the pancreatic duct and induced hemorrhagic pancreatitis. Opie also postulated that stones could affect the opening of the pancreatic duct and cause obstruction leading to pancreatitis. The common channel

dogma and its implied presence of cholecystitis and cholelithiasis has continued to dominate thinking despite the fact that only a fraction of patients with or without pancreatic disease possess a common channel and that in autopsies of many patients with acute pancreatitis, there are no gallstones obstructing the pancreatic duct. Similarly, animal experiments in which anastomosis of bile duct to pancreatic duct does not produce pancreatitis have failed to alter the firm belief that bile is in some way responsible for acute pancreatitis [003].

Alcoholic pancreatitis

In the late 18th and early 19th century alcohol for the first time was suspected as an etiologic factor in pancreatitis. Fleischmann, in 1815, described the case of a young alcoholic who developed repeated bouts of abdominal pain, nausea, and vomiting, an affliction to which he eventually succumbed. At autopsy, he was noted to have a scirrhous pancreas suggesting recurrent attacks of pancreatitis eventually leading to chronic pancreatitis [058]. The term "drunkard's pancreas" was coined by Friedreich in 1887, noting that "general, chronic interstitial pancreatitis may result from excessive alcoholism" [059]. Symmers [060] performed autopsies on 31 alcoholic patients who died suddenly and noted acute pancreatitis in the absence of gallstones. Nearly half a century later, Owens and Howard [061] clearly made the distinction between gallstone and alcoholic pancreatitis and described pancreatic calcifications in chronic alcoholic pancreatitis.

Despite the prevalence of alcohol-induced pancreatitis, the pathogenesis remains to be elucidated. Clinical observations of chronic pancreatitis in alcoholics were substantiated by experimental work in dogs by Sarles et al [062] where single exposure to alcohol did little damage to the gland, but chronic exposure resulted in changes of chronic pancreatitis [063]. However, further autopsy studies in humans have identified patients who had severe alcohol-induced acute pancreatitis with no underlying features of chronic pancreatitis, suggesting that, at least in a minority of patients, alcohol induces acute pancreatitis [064, 065]. Later animal studies have demonstrated that alcohol increases the sensitivity of the pancreas to hyperstimulation-induced zymogen activation and, consequently, pancreatitis [066, 067]. However, an understanding of the acute effects of alcohol on the acinar cell, the adaptive responses to chronic alcohol consumption, and the inciting factors that lead to recurrent acute pancreatitis and factors that predispose certain alcoholics to develop chronic pancreatitis remains limited [068]. In addition, hyperlipidemia, which is frequently present in the setting of alcoholism, may play a part in the pathogenesis of alcoholic pancreatitis [069].

Biochemical diagnosis

Up until the early 20th century, the diagnosis of acute pancreatitis was made either clinically or at autopsy. In 1908, Julius Wohlgemuth [070] from the Institute of Pathology at the Royal University of Berlin introduced a biochemical method for quantitative determination of the pancreatic enzyme diastase (amylase) in the serum. In 1929, Robert Elman, from St Louis, reported in 8 patients the correlation between acute epigastric pain secondary to pancreatic disease and elevation of blood amylase and subsequent relief of symptoms and a corresponding normalization of the serum amylase values thereby establishing the use of serum amylase as a marker for pancreatic inflammation [071]. Despite multiple improvements in technique, measurement of serum amylase to diagnose acute pancreatitis has continued to have significant limitations because there are multiple nonpancreatic causes of hyperamylasemia and because of the short-lived nature of amylase elevations in acute pancreatitis. The ability to measure pancreatic isoamylase [072] and macroamylase [073] has increased the specificity of amylase measurement in the diagnosis of acute pancreatitis. Determination of lipase, a more specific enzyme, was introduced by Cherry and Crandall [074] in 1932, and Comfort [075], in 1935, reported elevations of blood lipase in 17 of 20 patients with acute pancreatic disease. It was soon apparent that although amylase

and lipase were useful diagnostic tests, they had little utility in determining the severity or natural history of an attack of acute pancreatitis [076]. The measurement of various enzymes such as trypsin [077, 078], elastase [079], carboxypeptidase [080], and many others has been proposed, but to date, an accurate biochemical determination of the diagnosis and severity of acute pancreatitis remains elusive and successive generations of physicians have had to continue to rely on their clinical acumen in diagnosing and managing this disease.

Classification of acute pancreatitis

Early attempts to classify pancreatitis were primarily descriptive of the clinical and pathological features. Classification efforts such as those by Joske, Howard, and Dreiling, and Blumenthal and Probstein focused on the etiology of pancreatitis but were not widely applicable to clinical practice [081].

Beginning in 1974, John HC Ranson and surgical colleagues at New York University Medical Center proposed a set of objective criteria, which came to be referred to eponymously as the Ranson criteria, based on clinical and biochemical variables at presentation and 48 hours later [082, 083]. These criteria were widely adopted and the initial criteria were modified by various investigators, but the primary shortcomings of a 48-hour delay and the need for various laboratory tests to estimate the clinical course of a patient could not be improved [084]. Although later scores were an advance over the Ranson criteria in an objective assessment of severity and organ dysfunction, clinical applicability has been limited given that derivation of these scores is relatively complicated.

In addition to the various clinical prognostic and severity criteria, there have been efforts to establish a clinically based classification system for the protean manifestations of acute pancreatitis. A classification based on morphology was proposed in 1963 by a panel of experts who met in Marseille, and they primarily distinguished attacks of acute pancreatitis from chronic pancreatitis [085]. This classification was revised twice thereafter, but the focus of the changes was on classifying the various forms of chronic pancreatitis [086]. The first major effort to classify the various manifestations and outcomes of acute pancreatitis was the Atlanta classification proposed at an international symposium [087] in 1992. Criteria were proposed for severe acute pancreatitis, and these incorporated organ failure as a central determinant underscoring the improved understanding of the systemic burden of acute pancreatitis. Definitions were also proposed for interstitial pancreatitis, necrotizing pancreatitis, pseudocyst, and infected pancreatic necrosis.

The rapid advances in contrast-enhanced computed tomography (CT) have been critical in evaluating pancreatic necrosis and peripancreatic complications. In 1985, a grading system based on CT appearance of the pancreas and peripancreatic fluid collections was proposed by Balthazar et al [088] from John Ranson's group at the New York University Medical Center, and this remains the only widely applied radiologic grading system to date.

Attempts to treat acute pancreatitis

The limited recognition and understanding of pancreatic diseases up until the late 19th century meant that various empiric remedies were used in the treatment of these diseases. In his treatise on pancreatic diseases published in 1835, JJ Bigsby [019] noted that "inflammatory diseases of this organ do not run their course rapidly" and recommended limited bleeding to be achieved by the placement of a "dozen leeches to the abdominal parietes immediately over the seat of the pancreas." He advised against the use of stimulants such as mercury, noting somewhat presciently that "if the secretion of the inflamed organ be increased, while the canal for its discharge is closed up, nothing but mischief can result."

In the late 19th century, exploratory laparotomy gained momentum both to make a diagnosis of acute pancreatitis and to drain pancreatic abscesses and, in some instances, debride necrotic tissue. Proponents of early surgical intervention including Senn, Körte, and Moynihan, although during the same period, were no less authorities than Fitz and Mikulicz, advocated conservative management [003, 089].

The fervor for early surgical intervention was reversed after Gerhard Katsch's (1887-1961) report, that during World War I and, subsequently, thereafter, that the number of patients with acute pancreatitis declined, and he attributed this to the starvation prevalent around this time [003]. The introduction of the assay for amylase also led to the recognition of milder forms of the disease and the spontaneous recovery of many patients with acute pancreatitis. Conservative treatment became established after Paxton and Payne reported, in a series of more than 300 patients, a mortality rate of nearly 45 percent in patients treated surgically compared with 23 percent in those patients treated conservatively [090].

Beginning in the 1950s, the tide again turned to operative management as a means to treat patients with severe acute pancreatitis. Both in Europe and in the United States, pancreatic resection was routinely performed early in the course of patients with severe acute pancreatitis to remove necrotic material despite mortality rates of 60-70 percent after such treatment. Indeed, in 1963, George Watts, a surgeon in Birmingham, successfully treated a patient experiencing "fulminant pancreatitis" and in shock with a total pancreatectomy. Although this operation initially gained support and was widely used, the appalling mortality rate soon became evident and gave way to more cautious approaches in the late 1980s [010].

The most noteworthy achievements in the treatment of acute pancreatitis have been the advancements in supportive care including nutritional support, intensive care, and management of shock and organ failure. The introduction of total parenteral nutrition (TPN) by Dudrick et al [091] vastly improved the ability to sustain critically ill patients, and TPN rapidly became a standard approach in patients with severe acute pancreatitis. More recently, the focus has shifted to enteral nutrition because there is increasing evidence to suggest that it is safer, easier, as effective, and less expensive compared with TPN [092]. However, the issue of "resting the gland" is still to be resolved, and there continues to be debate about the relative merits of nasojejunal versus nasogastric feeding and the use of elemental formulas to minimize stimulation of the pancreas [010].

The history of pharmacological approaches to treat acute pancreatitis and its complications is composed of a litany of failed trials dating back to the 1920s starting with the use of enzyme inhibitors such as quinine. Other medications that have been studied include aprotinin, which was even marketed commercially but eventually shown to have no benefit [093] antifibrinolytics [094], anticholinergics including atropine, H_2-receptor antagonists, proton pump inhibitors, somatostatin, and octreotide [010]. Of these, somatostatin and octreotide were extensively studied, but controlled trials have indicated little or no benefit [095, 096]. Protease inhibition has also been investigated, and although gabexate mesylate, an antiprotease drug, has shown some promise in decreasing complication rates, clinical use of this drug is limited [096].

Gallstone pancreatitis

The report of Classen et al [097] on elective endoscopic papillotomy and removal of common bile duct stones opened up new frontiers in the treatment of gallstone pancreatitis and provided an alternative to surgery. Safrany and Cotton [098] popularized emergent endoscopic sphincterotomy and stone extraction to treat acute gallstone pancreatitis. The

first randomized trial evaluating the role of endoscopic sphincterotomy was performed by Neoptolemos et al [099] and reported an overall reduction in the complication rate in the group randomized to endoscopic treatment. Several studies followed, and it gradually became clear that not all patients with biliary pancreatitis need emergent endoscopic sphincterotomy, and currently, this approach is advocated for patients with concomitant cholangitis, biliary obstruction, or severe organ dysfunction [010].

John Beard

The British developmental biologist John Beard, DSc (1858-1924) is little remembered today. Yet, he made outstanding contributions to the life sciences. Beard deserves to be included among the leading biologists of the late 19th and early 20th century. He has been hailed as a forerunner of the present-day theory of the cancer stem cell. He was the first to point to the parallels between cancer and the trophoblastic cells that envelop and nourish the embryo, characterizing cancer as "irresponsible trophoblast." He pointed out that the initiation of fetal pancreatic function coincided with a reduction in the invasiveness of trophoblast, which otherwise might progress to clinical cancer (i.e. choriocarcinoma). Based on the above propositions, he recommended the therapeutic use of pancreatic enzymes in treating cancer and other diseases. This therapy created a worldwide controversy, and although rejected in his day, persists in the world of complementary and alternative medicine today [100].

In the early 20th century, advocacy of the enzyme therapy of cancer was primarily the work of one man, John Beard, DSc (1858-1924). He and his collaborators made a determined effort to establish this mode of therapy, especially in the years 1905 to 1911. Despite a brief flowering of international interest, Beard's efforts came to naught. During the 20th century, there was a succession of American researchers who continued to investigate this topic. This included Marshall William McDuffie, MD (1882-1945), Frank LeForest Morse, MD (1876-1953), Franklin Lloyd Shively, MD (1887-1971), and William Donald Kelley (1926-2005). In central Europe, India, and other parts of the globe, the use of pancreatic enzymes as an adjuvant treatment for cancer has become a fairly routine practice, at least among those doctors who utilize complementary and alternative medicine (CAM). It is also a well-established method for reducing inflammation and mitigating the adverse effects of cytotoxic treatment [101].

Pancreatic surgery

The first reliable report of pancreatic surgery in man and the cases that followed for the next years thereafter were confined to treatment of large pancreatic cysts with the usual preoperative misdiagnosis of the underlying disease. Fiedrich Wilhelm Wandesleben, a general physician in Stromberg, German, reporter a previous healthy 28 year old male who suffered blunt trauma to the abdomen in November 1844. The patient seemed to recover with the existing treatment, however, developed a palpable abdominal mass in two weeks. On December 4, 1844, an incision was made into the mass through the abdominal wall. After initial evacuation of pus, a clear watery substance welled up from the wound. Probing suggested a narrow channel trackning deep into the body cavity. Over the next 5 months clear fluid continued to exit from the wound. The fistulous tract started to close, but the patient developed malaise and died eventually of respiratory failure. Examination of the abdominal cavity demonstrated a smooth surfaced cavity within the head of pancreas with a narrow tract to the abdominal incision site.

Between 1860 and 1880, with the availability of ether anesthesia and Lister antisepsis, more abdominal operations in general and few incidental operations on the pancreas were

performed. In 1880, Carl Thiersch of Leipzig, Germany, reported the first possible survivor of pancreatic surgery. A 38 year old male after initial operation for a presumed abdominal wall abscess by an unnamed physician, underwent delayed operative drainage of 3 liter of dark, chocolate-colored fluid. A persistent fistula with drainage of clear fluid followed thereafter. Thiersch's probing and dilatation of the fistula demonstrated a tract heading toward the region of the pancreatic tail.

The first case of chemical diagnosis of pancreatic fistula in humans was published by Diedrich Kulenkampff of Bremen, Germany. He performed a trocar drainage of a presumed ecchinococcal cysta of the liver in 1881. The resultant persistent fistula caused maceration of the skin. Chemical analysis revealed alkaline character with an albumin precipitate on heating. The fluid was able to breakdown starch, protein and fat and in the absence of the bile led to the relatively confident diagnosis of pancreatic juice.

Pancreatic cysts

The resection of pancreatic cysts was apparently not considered feasible until Karl von Rokitansky, a gynecologic surgeon in Vienna, attempted a cystectomy in 1881. During partival resection of a pancreatic cyst in the lesser sac there was intraoperative disruption of transverse colon, spillage of fluid into the peritoneal cavity and major hemorrhage. The cysta was eventually removed, but the patient died of sepsis ten days later. The autopsy showed that the cyst originated from the head of pancreas.

On December 2, 1881, Nathan Bozeman operated on a 41 year old femal admitted to Women's Hospital in New York with the presumed diagnosis of a large ovarian cyst. Five liters of light brownish fluid was drained intraoperatively from the cyst. The cyst was found to be mobile within the abdominal cavity with a pedicle connecting to the tail of pancreas. The pedicle was ligated and the cyst excised. Postoperative pain was controlled with rectal administration of tinctures of quinine, beer-juice, opium and brandy. The early postoperative course was unremarkable but the long term outcome after discharge is unknown.

The world's first planned pancreatic surgery was performed by Karl Gussenbauer of Prague on December 22, 1882. The patient was a 40 year old male who developed epigastric pain and a large palpable mass after extensive consumption of alcohol. Air inflation of the stomach and colon showed that the tumor was located behind both organs. This observation led Gussenbauer to the assumption that the tumor was likely caused by a pancreatic cysta. Due to the detoriorating condition of the patient, Gussenbauer performed marsupialization of the cyst wall to the abdominal wall with placement of a large drain and packning into the cavity. The pancreatic healed gradually and the patient remained well for at least 8 years after surgery. During his career, Gussenbauer operated on at least three smilar patients with pancreatic cysts.

After Gussenbauer's publication, the number of operations for pancreatic cysts increased rapidly. Kuster was able to collect 13 published cases reported within 5 years after Gussenbauer's initial presentation. By 1900, there were 149 reported cases which include not only pseudocysts, but also retention and proliferative cysts. At that time mortality for cyst excision was close to 19 percent and for external marsupialization was 3 percent. Procedures such as cystoduodenostomy by Louis Ombredanne in 1911, cystogastrostomy by Rudolf Jedlicka 1921, cystjejunostomy by Adolf Henle in 1923 (but first reported by Otto Hahn in 1927) introduced new standards in pancreatic surgery.

First pancreatic resections

The first true pancreatic resection in humans was not performed until 1882. Prior to that, only

anecdotal reports of pancreatic resection for pancreatic protrusion after penetrating abdominal trauma were reported. Distal pancreatectomy was the first reported anatomic resection of pancreatic parenchyma in humans by Friedrich Trendelenburg of Bonn, Germany, on July 16, 1882. The patient was a 44 year old female with a giant mass in the left upper quadrant. Trendelenburg resected the retroperitoneal mass along with the pancreatic tail from which the mass seemed to originate. The operation was complicated by a splenic injury requiring splenectomy. The proximal pancreatic remnant was closed with suture ligature. Histology revealed a spindel cell carcinoma. The postoperative course was complicated by wound infection and malnutrition. The patient insisted on going home but died there later of respiratory failure. By 1910, distal pancreatectomy was reported in another five patients, two of who died postoperatively.

Enucleation

The first reported enucleation of pancreatic mass was performed by Giuseppe Ruggi of Bologna on September 4, 1889. The patient was a 50 year female with physical findings of a large, mobile mass in the upper abdomen associated with epigastric disdomfort, constipation and malaise. At operation, ascites as well as a large soft tumor in proximity to the head of pancreas was fond. Histology showed an adenocarcinoma with adjacent glandular tissue.

Billroth, Codivilla and Halstedt

Several reports suggest that Theodor Billroth of Vienna undertook a presumed total pancreatectomy in 1884 with good outcome (anectotal by Arthur William Mayo Robson in a speech given to an international medical Congress in 1990). In June 5, 1885, Billroth also performed excision of a large pancreatic cysta originating from the body of pancreas, almost completely replacing it. Along with resection of the atrophic pancreas body, Billroth resected the splenic vessels, which was not recognized until after the surgery. The transected pancreas was not closed. This case represent the first reported true anatomic central pancreatic resection.

A landmark in pancreatic surgery was when Allesandro Codivilla of Imola, Italy, performed the first pancreatoduodenectomy on Februari 9, 1898. Codivilla never published the case, but his successor Bartolo Del Monte did, which was brought to attention by Louis Sauve in 1908. Codivilla operated on a 46 year old male who presented with 20 day history of epigastric distension and vomiting. On exploration he found a cancer involving stomach and pancreas and did distal gastrectomy, resection of portion of duodenum with head of pancreas and distal bile duct. The common bile duct and distal duodenal stump were oversewn. Intestinal continuity was established by a Roux-en-Y gastrojejunostomy and cholecystojejunostomy over a Murphy's buttons. The patient developed steatorrhea and died of cachexia 18 days after the operation.

On February 14, 1898, William Stewart Halsted undertook the first resection of an ampullary tumor in a 60 year old female with a six month history of painless jaundice, gallbladder distension and hepatomegaly. The operation included common bile duct exploration, transduodenal papillectomy with reanastomosis of pancreatic and bile duct and tube cholecystectomy. Three months later the patient developed jaundice on removal of tube cholecystostomy and cholecystoduodenostomy was done for terminal biliary stenosis.

Biliary-enteric anastomosis

The concept of bilioenteric drainage was introduced in 1880 when Theodor Billroth's former student Alexander von Winiwarter performed a cholecystocolostomy which was later revised to a cholecystojejunostomy. A successful cholecystojejunostomy in a patient with pancreatic

cancer was reported by Nestor Dimitrievic Monastyrski of St Petersburg, Russia, in 1987 and a cholecystoduodenostomy by Loui-Felix Terrier of Paris, France in 1889. In 1884, a choledochotomy was first attempted by Hermann Kummell of Hamburg, Germany, followed by a choldochoduodenostomy by Bernhard Riedel of Jena, Germany, in 1888 with fatal outcome in both cases. A successful choledochotomy was performed by New York surgeon Robert Abbe in 1889 and in 1891, Oskar Sprengel of Dresden, Germany, published the first successful choledochoduodenostomy. The first successful Roux-en-Y cholecystojejunostomy was performed by Ambrose Monprofit of Angers, France, in 1904 a Roux-en-Y choledochojejunostomy by Robert Dahl of Stockholm, Sweden, in 1908.

Managing the pancreatic remnant

The first pancreatic head resection with transaction of the pancreatic duct was performed by Domenico Biondi of Cagliari, Italy, in 1894. He excised a fibroadenoma from the lower two-thirds of the head of pancreas and reapproximated the duodenum and the pancreatic remnant. The postoperative course was complicated by an early biliary fistula and later by a pancreatic fistula which eventually resolved.

Pancreatic suturing was not published until 1905, Wien Carl Garre from Königsberg, Preussia, reporter a patient with completed tranaction of pancreas from blunt trauma, where the fully separated edges of the pancreatic halves were reapproximated successfully through placement of small silk sutures in the pancreatic capsule. The duct was not sutured and the result was a pancreatic fistula which resolved in two months along with complete recovery, This technigue was applied to a midbody resection by John Finney of Baltimore, Maryland, in 1909 as well as in the first successful partival pancreatoduodenectomy by Oskar Erhardt of Köningsberg in 1907. This was a 32 year old female who had undergone gastrojejunostomy recently for what was thought to be an unresectable cancer of pylorus adherent to a second mass in the head of pancreas. She came back with vomiting and was reexplored on August 4, 1907. Oskar Ehrhardt resected the gastric antrum, pylorus, duodenal bulb, part of second part of duodenum and large parts of the head of pancreas within its capsule. A remnant of pancreas was left posterior to a partially transected pancreatic duct. The bile duct was spared and the edges of the pancreatic capsule were reapproximated to cover the pancreatic duct. The postoperative course was complicated by a leak which was reasonably controlled. However, the patient died of recurrent disease after five months.

In the same year Abel Desjardins of Paris published a technique of end-to-end double layer invaginating pancreatojejunostomy smilar to today's telescoping metod.

Kausch and Hirschel

Walther Kausch applied the technique of the Kocher moneuver in pancreatic surgery and did his first - and only - pancreatoduodenectomy in Berlin in June 15 in 1909 in a 49 year old patient with anorexia, weight loss, malnourishment, and jaundice. The operation consisted of a loop cholecystojejunostomy with a Braun anastomosis over a Murphy's button and two months later a resection and a two-layer pancreatojejunal anastomosis. The patient had a leak which healed spontaneously, but the patient died nine months later of sepsis from cholangitis.

A successful one stage partival pancreaoduodenectomy was performed by Georg Hirschel of Heidelberg, Germany, in 1912 for ampullary carcinoma. The patient survived for one year but died a year later from unknown cause.

Whipple and Braunschweig

Allen Oldfather Whipple performed a pylorus-preserving partial pancreatoduoden-ectomy in 1935. All pancreatoduodenectomies performed prior to 1937 were nonanatomic resections removing only part of the head of pancreas and duodenum. On February 11, 1937, Alexander Braunschweig performed a two-stage pylorus-preserving pancreatoduodenectomy for pancreatic carcinoma at the University of Chicago Hospital. This was the first true anatomic resection with complete removal of the pancreatic head to the right of the superior mesenteric vein. On March 6, 1950 Allen Whipple operated at New York's Presbytarian Hospital on a patient thought to have carcinoma of the antrum of stomach. The stomach was already divided before it became apparent that the origon of the tumor was head of pancreas. That operation was most likely the first anatomic one-stage pancreato-duodenectomy with antrectomy and complete removal of the duodenum and marks the beginning of modern pancreatic head resection.

Rockey and Priestly

A true total pancreatectomy appears to have been first performed by Eugene Rockey of Portland, Oregon, on June 22, 1942, but the patient died 15 days later of bile peritonits. Three weeks later, on July 15, 1942, James Priestly of Rochester, Minnesota, performed a total pancreatectomy on a 40 year old women who suffered from hypoglycemic episodes. He could not find the pancreatic tumor on exploration and therefore made the radical decision to perform a total pancreatectomy for what turned out to be a 1 cm insulinoma. The patient survived for 29 years before dying of cholangitis.

Pancreatic duct drainage in chronic pancreatitis and pancreatic cancer

With the evolution of understanding of pathophysiology of chronic pancreatitis, Goethe Link of Indianaplois, Indiana, performed in March 1910 an exploration of the pancreatic duct, extracted a pancreatic duct stone and created an external distal tube pancreatostomy with a good long-term outcome. Short segment, loop pancreatojejunostomies stented by a T-tube was performed by Richard Cattell for patients with pain from an unresectable pancreatic cancer in the 1940s.

In 1951, William Longmire performed a caudal pancreatectomy with end-to-end pancreatojejunostomy later popularized by Merlin DuVal in 1954. In 1958, Charles Puestow and William Gillesby of Chicago, Illinois, modified this procedure to a caudal pancreatectomy with splenectomy, and extended longitudinal opening of the pancreatic duct and Roux-en-Y end-to-side or side-to-side pancreatojejunostomy. In 1960, Phillip Partington and Robert Rochelle of Cleveland, Ohio, simplified the procedure by eliminating the caudal pancreatectomy and splenectomy. These pancreatic duct drainage procedure procedures paved the way to the lateral pancreatojejunostomy with limited nonanatomic pancreatic head resection described by Charles Frey in 1987 and the duodenum-preserving partival pancreatic head resection described by Hans Beger in 1980.

Pancreatic transplantation

Ever since the first transplant in 1967 by Kelly and Lillihei, University of Minnesota has been in forefront. The first pancreas islets autotransplant in the late seventies, successful pancreas transplant series, livning donor pancreas transplant, living simultaneous kidney pancreas transplants open as well as laparoscopic are some of the more recent accomplishments reported from this center.

Modern pancreatic history

Howard Reber

Dr. Howard Reber is a world-renowned pancreatologist in the area of basic pancreatic physiology and the managementof pancreatic diseases. As a 3rd year medical student, he became fascinated with both the physiology and function of the pancreas, as well as its diseases. During my surgical training at the University of Pennsylvania, he had the fortune to be the recipient of a NationalInstitutes of Health Training Grant administered by the National Institute of General Medical Sciences. Dr. Frank Brooks, who was then Chief of Gastro-enterology at the University of Pennsylvania, arranged a meeting with Dr. Henry Janowitz, a gastroenterologist who had done pioneering work in the pancreas at Mt. Sinai Hospital in New York, late in the summer of 1966. He started investigating the role of the pancreatic ducts in the secretion of water and electrolytes by the gland together with Dr. David Dreiling. He then went to the Peter Bent Brigham Hospital in Boston. Over the years, he has devoted his research efforts to several different problem areas. The first related to studies of basic physiology and the processes of secretion, as exemplified by the micropuncture, and later on to both chronic pancreatitis and pancreatic cancer [102].

John Howard

In 1942 John Howard as a sophomore student in the University of Pennsylvania School of Medicine, was studying pathology. A senior student, suggested the study of the anatomy of the pancreatic ampulla: “Is reflux of bile into the pancreatic ducts anatomically possible?” Of 150 dissections a common channel’ was found in at least 50 percent (a confirmatory finding). In the early days, pancreatitis was considered by most clinicians to be a single disease. Of course this isn’t true. Like pneumonia or gastroenteritis it consists of many diseases. In 1946 John Howard an co-worker reviewed the records of all 80 patients with acute pancreatitis who had been admitted to the University of Pennsylvania Hospital in the previous 25 years (1922–1946 inclusive). The hospital mortality rate had been about 30 percent. The diagnosis on each patient had been made at laparotomy or autopsy. Although not so classified, all were idiopathic in that era. Fifty-three (two thirds) of the patients had had gallstones, but pancreatitis had not been attributed to the gallstones. Furthermore, of those patients having undergone laparotomy, the majority had had a cholecystostomy regardless of the presence or absence of gallstones. Later, Dr. George Jordan, Jr. and John Howard were young surgical colleagues at Baylor University in Houston. In systematically reviewing the pancreatitis patients, the alcoholic patients at the Veterans Administration were found to have quite a different disease from those nonalcoholic patients at the Charity Hospital. Acute pancreatitis was not a disease. It was clearly a reflection of multiple diseases, perhaps of a hundred or more! Each differed in its etiology, natural history and essential treatment [103].

Katsusuke Satake

Professor Dr Katsusuke Satake died on March 21, 2009, due to lung cancer. Dr Satake was considered by many of us as an Ambassador for Pancreatic Research in Japan to the international community. He was a pioneering pancreatic investigator and surgeon and an international lecturer, writer, and editor. He searched within many Japanese forums for young investigators and colleagues to journey with him in his research. Dr Katsusuke Satake was born in Osaka in 1935. He graduated from medical school at Osaka City University in 1962, whereupon he immediately entered a 2-year internship at the US Air Force Hospital in Tachikawa, Japan. Dr Satake continued his clinical training and research at the Department of Surgery, Osaka City University, and later became the Chief Resident of that department. In 1970, he decided to join Dr John M. Howard’s group as a Research Assistant in the Department of Surgery at Hahneman Medical College in Philadelphia, where he began his

research in pancreatology. Dr Satake's initial research work on acute pancreatitis in dogs was published in Archives of Surgery and Annals of Surgery. Upon his return to Osaka City University in 1972, he continued his research in pancreatology by using rat and hamster models of pancreatic carcinogenesis as well as dog models of acute pancreatitis. Dr Satake was promoted to Assistant Professor in 1973, Lecturer in 1979, and subsequently to Associate Professor in 1989. During these highly productive periods of research in pancreatology and investigations on the pathophysiology and treatment of acute pancreatitis, carcinogenesis, chemoprevention, early detection, and effective treatment of pancreatic cancer, he used various technologies, including hormone assays, electron microscopy, hydrogen gas clearance, and tumor markers. In addition, Dr Satake used his vast knowledge and leadership experience as a parttime faculty member at the Graduate School of Medicine, Kyoto University, from 2000 to 2006. He resigned from Osaka City University in 2006 and was appointed Director of Otori Clinic, Sakai, Osaka, Japan [104].

PANCREATIC DEVELOPMENT, EMBRYOLOGY and ANATOMY

Regenerative medicine, including cell-replacement strategies, may have an important role in the treatment of type 1 and type 2 diabetes, both of which are associated with decreased islet cell mass. To date, significant progress has been made in deriving insulin-secreting beta-like cells from human ES (embryonic stem) cells. However, the cells are not fully differentiated, and there is a long way to go before they could be used as a replenishable supply of insulin-secreting beta-cells for transplantation. For this reason, adult pancreatic stem cells are seen as an alternative source that could be expanded and differentiated ex vivo, or induced to form new islets in situ. In one issue of the Biochemical Journal, Mato et al. used drug selection to purify a population of stellate cells from explant cultures of pancreas from lactating rats. The selected cells express some stem-cell markers and can be grown for over 2 years as a fibroblast-like monolayer. When plated on extracellular matrix, along with a cocktail of growth factors that included insulin, transferrin, selenium and the GLP-1 (glucagon-like peptide-1) analogue exendin-4, the cells differentiated into cells that expressed many of the phenotypic markers characteristic of a beta-cell, and exhibited an insulin-secretory response, albeit weak, to glucose. The ability to purify this cell population opens up the possibility of unravelling the mechanisms that control self-renewal and differentiation of pancreatic cells that share some of the properties of stem cells [105].

Factors influencing development

Regenerating gene I

Pancreatic regenerating gene I (reg I) has been implicated in cellular differentiation. Acinar cells can transdifferentiate into other pancreatic-derived cells, and it was postulated that changes in intracellular levels of reg I would affect the state of differentiation transfected AR42J cells with a plasmid containing the entire coding sequence of reg I and isolated clones with complementary DNA in sense (SS) or antisense (AS) orientation. It was found that in acinar cells, reg I overexpression is linked to acinar cell differentiation, whereas inhibition of reg I leads to beta cell and possibly ductal phenotype. Reg I expression in acinar cells is important in maintaining pancreatic cell lineage, and when decreased, cells can dedifferentiate and move toward becoming other pancreatic cells [106].

Transforming growth factor-beta (TGF-beta)

Studies of the formation of pancreas and liver progenitors have focused on individual inductive signals and cellular responses. Here, it was investigated how bone morphogenetic protein, transforming growth factor-beta (TGF-beta), and fibroblast growth factor signaling pathways converge on the earliest genes that elicit pancreas and liver induction in mouse embryos. The inductive network was found to be dynamic; it changed within hours. Different signals functioned in parallel to induce different early genes, and two permutations of signals induced liver progenitor domains, which revealed flexibility in cell programming. Also, the specification of pancreas and liver progenitors was restricted by the TGF-beta pathway. These findings may enhance progenitor cell specification from stem cells for biomedical purposes and can help explain incomplete programming in stem cell differentiation protocols [107].

Islet neogenesis-associated protein

Efforts to cure diabetes are now focused on restoring a physiologically-regulated population of insulin-producing cells to the patient. A number of animal models of beta cell regeneration

have been employed to study the mechanisms of the process. Islet neogenesis, the regeneration of pancreatic islets from pancreatic stem cells, is arguably the least fraught with barriers to widespread use as a therapy for diabetes. These animal models have led to the description of the reg family of proteins that appear to be related to islet regeneration. Islet neogenesis-associated protein (INGAP) is an initiator of islet neogenesis in animal models and a peptide sequence from INGAP carries the biological activity. INGAP peptide has been shown to stimulate an increase in beta cell mass in mice, rats, hamsters and dogs. INGAP is also found in the pancreas in human pathological states involving islet neogenesis. The peptide has been tested in human clinical trials, with success being reported. The evidence points to INGAP as a major factor in stimulating islet neogenesis, and, therefore, may play a significant therapeutic role in diabetes [108].

Connexins

Diabetes and the related metabolic syndrome are multisystem disorders that result from improper interactions between various cell types. Even though the underlying mechanism remains to be fully understood, it is most likely that both the long and the short distance range cell interactions, which normally ensure the physiologic functioning of the pancreas, and its relationships with the insulin-targeted organs, are altered. One review focused on the short-range type of interactions that depend on the contact between adjacent cells and, specifically, on the interactions that are dependent on connexins. The widespread distribution of these membrane proteins, their multiple modes of action, and their interactions with conditions/molecules associated to both the pathogenesis and the treatment of the 2 main forms of diabetes and the metabolic syndrome, make connexins an essential part of the chain of events that leads to metabolic diseases [109].

Diphtheria toxin gene A chain (DTA)

Cell lineage analysis is critical in understanding the relationship between progenitors and differentiated cells as well as the mechanism underlying the process of differentiation. In order to study the zebrafish endocrine pancreas cell lineage, transgenic expression of diphtheria toxin gene A chain (DTA) under two cell type-specific promoters derived from the insulin (ins) and somatostatin2 (sst2) genes was used to ablate the two types of endocrine cells: insulin-producing beta-cells and somatostatin-producing delta-cells, respectively. It was found that ablation of beta-cells resulted in a reduction of not only beta-cells but also glucagon-producing alpha-cells; in contrast, delta-cells were largely unaffected. Ablation of delta-cells led to reduction of all three types of endocrine cells: alpha-, beta-, and delta. Interestingly, alpha-cells were more profoundly affected in both beta- and delta-cell ablations and were frequently reduced together with beta- and delta-cells. Thus, the current observations indicated differential interdependence of these three cell lineages. The development of zebrafish alpha-cells, but not delta-cells, is dependent on beta-cells, while the development of both alpha- and beta-cells is dependent on delta-cells. In contrast, the development of delta-cells is independent of beta-cells [110].

Cell-surface markers

It was developed a novel panel of cell-surface markers for the isolation and study of all major cell types of the human pancreas. Hybridomas were selected after subtractive immunization of Balb/C mice with intact or dissociated human islets and assessed for cell-type specificity and cell-surface reactivity by immunohistochemistry and flow cytometry. Antibodies were identified by specific binding of surface antigens on islet (panendocrine or alpha-specific) and nonislet pancreatic cell subsets (exocrine and duct). These antibodies were used individually or in combination to isolate populations of alpha, beta, exocrine, or duct cells from primary human pancreas by FACS and to characterize the detailed cell composition of human islet

preparations. They were also employed to show that human islet expansion cultures originated from nonendocrine cells and that insulin expression levels could be increased to up to 1 percent of normal islet cells by subpopulation sorting and overexpression of the transcription factors Pdx-1 and ngn3, an improvement over previous results with this culture system. These methods permit the analysis and isolation of functionally distinct pancreatic cell populations with potential for cell therapy [111].

Oxygen

Beyond its role as an electron acceptor in aerobic respiration, oxygen is also a key effector of many developmental events. The oxygen-sensing machinery and the very fabric of cell identity and function have been shown to be deeply intertwined. Here it was taken a first look at how oxygen might lie at the crossroads of at least two of the major molecular pathways that shape pancreatic development. Based on recent evidence and a thorough review of the literature, it was presented a theoretical model whereby evolving oxygen tensions might choreograph to a large extent the sequence of molecular events resulting in the development of the organ. In particular, it was proposed that lower oxygenation prior to the expansion of the vasculature may favour HIF (hypoxia inducible factor)-mediated activation of Notch and repression of Wnt/beta-catenin signalling, limiting endocrine cell differentiation. With the development of vasculature and improved oxygen delivery to the developing organ, HIF-mediated support for Notch signalling may decline while the beta-catenin-directed Wnt signalling is favoured, which would support endocrine cell differentiation and perhaps exocrine cell proliferation/differentiation [112].

Thyrotropin-releasing hormone

Thyrotropin-releasing hormone (TRH) is expressed in rodent and human adult pancreata and in mouse pancreas during embryonic development. However, expression of TRH receptors (TRHRs) in the pancreas is controversial. It was used quantitative reverse transcription-polymerase chain reaction to measure TRH and TRHR messenger RNA (mRNA). To study the effects of TRHR expression in a pancreatic progenitor population, it was expressed TRHRs in human islet-derived precursor cells (hIPCs) by infection with adenoviral vector AdCMVmTRHR. Thyrotropin-releasing hormone receptor signaling was measured as inositol phosphate production and intracellular calcium transients. Thyrotropin-releasing hormone receptor expression was measured by [3H]methyl-TRH binding. Apoptosis was monitored by release of cytochrome c from mitochondria. It was shown that TRH mRNA is expressed in human fetal and adult pancreata, and that TRHR mRNA is expressed in fetal human pancreas but not in adult human pancreas. Thyrotropin-releasing hormone receptors expressed in hIPCs were shown to signal normally. Most importantly, TRH treatment for several days stimulated apoptosis in hIPCs expressing approximately 400,000 TRHRs per cell. These findings suggest a possible role for TRH/TRHR signaling in pancreatic precursors to promote programmed cell death, a normal constituent of morphogenesis during embryonic development in humans [113].

Pancreatic anatomy and malformations

Ectopic pancreas

To describe the computed tomographic (CT) findings of ectopic pancreas and to identify the features that differentiate it from other similarly manifesting gastric submucosal tumors such as gastrointestinal stromal tumor (GIST) and leiomyoma, which are the most common gastrointestinal submucosal tumors a retrospective study investigated CT images of pathologically proved ectopic pancreases (n=14), GISTs (n=33), and leiomyomas (n=7) in

the stomach and duodenum. Analysis of the CT findings included evaluation of the location, contour, growth pattern, border, enhancement pattern, and enhancement grade of the tumor, as well as the presence of surface dimpling, prominent enhancement of overlying mucosa, and low intralesional attenuation. The attenuation of each lesion, the long diameter (LD), the short diameter (SD), and the LD/SD ratio were measured. The typical location (prepyloric antrum and duodenum), endoluminal growth pattern, ill-defined border, prominent enhancement of overlying mucosa, and an LD/SD ratio of greater than 1.4 were found to be significant for differentiating ectopic pancreas from other tumors. When at least two of these five criteria were used in combination, the sensitivity and specificity for diagnosing ectopic pancreas were 100 percent (14 of 14) and 83 percent (33 of 40), respectively. When four of these criteria were used, a sensitivity of 43 percent and a specificity of 100 percent were achieved [114].

Ectopic pancreatic tissue within a duodenal diverticulum has not been previously described in the English-language literature. It was reported a case of a 52-year-old woman who presented with a perforated duodenal diverticulum after upper endoscopy. Operative resection and repair of the perforated diverticulum was performed, and, on microscopic examination, ectopic pancreatic tissue was found within the diverticulum [115].

Circumportal annulare

There have been 6 cases of circumportal pancreas reported, and 2 of them had the main pancreatic duct in a retroportal dorsal portion. This extremely uncommon anomaly is asymptomatic and therefore incidentally discovered. For the surgeon, it is important to discover this during pancreatic resection so the pancreatic duct can be closed and fistula is avoided. It was now describe a third case where a circumportal pancreas had its main pancreatic duct passing under the portal vein. The duct was identified and ligated. A fistula did not occur [116].

Pancreas annulare

Annular pancreas is a rare embryonal abnormality. Its manifestation in adulthood is often pinpointed with a substantial delay, which is most often attributed to pancreatitis, biliary pathology or dyspepsia. It was presented a case of a 28-year-old woman who had exacerbating symptoms of high bowel obstruction from 20th week of pregnancy, progressing after premature delivery. Diagnostic work-up revealed partial annular pancreas compressing the duodenum. Despite attempts of conservative treatment, her state deteriorated to such an extent that surgery was indicated and gastrojejunal bypass created. Her postoperative recovery was uneventful. In cases in which symptoms of high bowel obstruction in pregnancy persist and prostration occurs, we suggest close monitoring and a more thorough diagnostic approach. The question remains whether annular pancreas presents a cause of pathologic findings, a cofactor, or a mere accidental diagnosis in the development of superposed pathologies [117].

The purpose of one study was to review the CT, MRI, and ERCP findings of annular pancreas in adults. A search of the radiology and ERCP databases at one institution for cases of annular pancreas in adults yielded the records of 42 patients who underwent 29 ERCP, 22 CT, and 13 MRI examinations. Nine of 24 (38 %) cases of annular pancreas detected with CT or MRI did not have a radiologically complete ring of pancreatic tissue surrounding the second part of the duodenum. Three of the nine patients (33 %) with radiologically incomplete annular pancreas and six of the 15 patients (40 %) with complete annular pancreas had gastric outlet obstruction. The presence of pancreatic tissue posterolateral to the second part of the duodenum had a high sensitivity (92 %) and specificity (100 %) for the presence of annular pancreas. The rates of pancreas divisum (37 %) and chronic pancreatitis (48 %) were high in this cohort. It was concluded that annular

pancreas can be diagnosed without the finding of a radiologically complete ring of pancreatic tissue. A crocodile jaw configuration of pancreatic tissue is suggestive of the presence of annular pancreas [118].

It was reported a rare case of a neonate with a duodenal stenosis due to the contemporary presence of an annular pancreas and wind sock web [119].

Polyspleni and short pancreas

The most common form of splenic anomaly with a concurrent short pancreas is polysplenia, which has been described in various studies in the radiological literature. However, splenic duplication has never been reported. It was now reported a case of splenic duplication associated with a short pancreas and pre-duodenal portal vein. This extremely rare case of splenic anomaly shows unique multidetector CT findings that are distinguishable from a splenic lobulation or cleft [120].

Double common bile duct

It was presented a case of double common bile duct. Specifically, it was found a common bile duct that was divided into two distinct ducts, one the main and the other the accessory duct, during its course downwards. The two bile ducts had a parallel course emerging from the common bile duct after its formation and reuniting just above the head of the pancreas. Finally, they drained into the second portion of the duodenum at the site of major duodenal papilla. This anomaly is of great importance because the duplication of the common bile duct can lead to severe intraoperative injury to one of the two common bile ducts, which can be mistaken for the cystic duct and be ligated [121].

Anomal pancreatic duct system

The formation of the pancreatic duct system is the result of the fusion of 2 embryonic buds, the ventral and dorsal primordia. Frequently, this fusion process is localized in the pancreatic head; variations, however, may account for the structural diversity of the duct system. Pancreatic duct anomalies and diversity of body and tail are thought to be casuistic. Ninety-nine consecutive adult autopsies with reference to macroscopic anomalies in the distal part of the gland were evaluated. Pancreatograms were performed after large duodenal papilla cannulation. Ducts parallel to gland axis with a diameter of at least one third of the main pancreatic duct at the junction point and aberrant duct with different shapes or abnormal third-degree ductuli architecture were noted. The study revealed a 10 percent frequency of main pancreatic duct diversity in the pancreatic corpus and tail. Eleven atypical ducts were visible, 9 cranially and 2 caudally from the main pancreatic duct [122].

Agenesia of the dorsal pancreatic neck, body and tail

Morphogenesis of the pancreas is a complex process; nevertheless, congenital anomalies are rare. At embryogenesis, the pancreas develops from the endoderm-lined dorsal and ventral buds of the duodenum. The ventral bud gives rise to the lower head and uncinate process of the pancreas; whereas, the dorsal bud gives rise to the upper head, isthmus, body, and tail of the pancreas. Rarely, developmental failure of the dorsal pancreatic bud at embryogenesis results in the agenesis of the dorsal pancreas-neck, body, and tail. Even rarer is the association of pancreatic tumors with agenesis of the dorsal pancreas. In addition to citing one case, it was provided a comprehensive review on agenesis of the dorsal pancreas and its association with pancreatic tumors [123].

Fatty pancreas

To investigate the clinical implications of lipid deposition in the pancreas (fatty pancreas) 293 patients who had undergone abdominal computed tomography (CT) and sonography were studied. Fatty pancreas was diagnosed by sonographic findings and subdivided into mild, moderate, and severe fatty pancreas groups comparing to the retroperitoneal fat echogenicity. Fatty pancreas was associated with higher levels for visceral fat, waist circumference, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, high density lipoprotein, free fatty acid, gamma-GTP, insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) than the control group ($P < 0.05$). HOMA-IR, visceral fat, triglyceride, and ALT also tended to increase with the degree of fat deposition in the pancreas on sonography. In a multivariate logistic regression analysis, HOMA-IR, visceral fat, and ALT level were independently related to fatty pancreas after adjustment for age, body mass index, and lipid profile. The incidence of metabolic syndrome in the fatty pancreas group was significantly higher than in the control group, and the numbers of metabolic syndrome parameters were significantly higher in the fatty pancreas group. It was thus concluded that sonographic fatty pancrease showed higher insulin resistance, visceral fat area, triglyceride, and ALT levels than normal pancreases. Fatty pancreas also showed a strong correlation with metabolic syndrome [124].

Spleno-pancreatic fusion

It was reported multidetector computed tomography findings of fusion between the spleen and the distal pancreas with magnetic resonance imaging findings, which has not been reported before. Diagnosis of splenopancreatic fusion can be important in patients who will undergo splenectomy or distal pancreatectomy to avoid possible complications [125].

PANCREATIC PHYSIOLOGY

Sphincter of Oddi

The most common functional disorder of the biliary tract and pancreas relates to the activity of the Sphincter of Oddi. The Sphincter of Oddi is a small smooth muscle sphincter strategically placed at the junction of the bile duct, pancreatic duct, and duodenum. The sphincter controls flow of bile and pancreatic juices into the duodenum and prevents reflux of duodenal content into the ducts. Disorder in its motility is called Sphincter of Oddi dysfunction. Clinically this presents either with recurrent abdominal biliary type pain or episodes of recurrent pancreatitis. Manometry may identify the motility abnormalities, the most clinically significant being an abnormally elevated basal pressure. The most effective treatment once an abnormal basal pressure is identified is division of the sphincter. This is associated with good long-term results [126].

Modulatory drugs of gastrointestinal (GI) motility are a possibility for use to relieve the main clinical presentation of sphincter of Oddi (SO) dysfunctions which are not easily distinguished from those occurring in high prevalence functional GI disorders. The aim of one study was to investigate the effects of GI motility modulators including pinaverium, domperidone, trimebutine, and tegaserod on the contractile activity of SO stimulated by carbachol in the rabbit. The contraction responses precontracted by carbachol (0.1 μM) of in vitro rabbit SO rings were evaluated before and after the addition of a series concentration (10^{-13} to 10^{-3}M) of pinaverium, domperidone, trimebutine, and tegaserod. Pinaverium induced a concentration-dependent relaxation of isolated SO rings precontracted with carbachol (0.1 μM). Tegaserod did not significantly effect SO motility, but domperidone seemed to stimulate SO contractions. At low doses (10^{-13} to 10^{-7}M), trimebutine stimulated SO contraction; however, high doses (10^{-6} to 10^{-3}M) of trimebutine inhibited SO motility. It was concluded that pinaverium totally inhibits contractions induced by carbachol and tegaserod has no effect on carbachol-induced contractions. Domperidone stimulates contractions induced by carbachol. Trimebutine could either stimulate or inhibit SO contractions depending on its dosage [127].

Feeding

The complex control of food intake and energy metabolism in mammals relies on the ability of the brain to integrate multiple signals indicating the nutritional state and the energy level of the organism and to produce appropriate responses in terms of food intake, energy expenditure, and metabolic activity. Central regulation of feeding is organized as a long-loop mechanism involving humoral signals and afferent neuronal pathways to the brain, processing in hypothalamic neuronal circuits, and descending commands using vagal and spinal neurons. Sensor mechanisms or receptors sensitive to glucose and fatty acid metabolism, neuropeptide and cannabinoid receptors, as well as neurotransmitters and neuromodulators synthesized and secreted within the brain itself are all signals integrated in the hypothalamus, which therefore functions as an integrator of signals from central and peripheral structures. Homeostatic feedback mechanisms involving afferent neuroendocrine inputs from peripheral organs, like adipose tissue, gut, stomach, endocrine pancreas, adrenal, muscle, and liver, to hypothalamic sites thus contribute to the maintenance of normal feeding behavior and energy balance. In addition to transcriptional events, peripheral hormones may also alter firing and/or connection (synaptology) of hypothalamic neuronal networks in order to modulate food intake. Moreover, intracellular energy sensing and subsequent biochemical adaptations, including an increase in AMP-activated protein kinase activity, occur in hypothalamic neurons. Understanding the regulation of appetite is clearly a major research effort but also seems promising for the development of novel therapeutic strategies for obesity [128].

Studies of pancreatic duct secretion

The pancreatic ductal tree conveys enzymatic acinar products to the duodenum and secretes the fluid and ionic components of pancreatic juice. The physiology of pancreatic duct cells has been widely studied, but many questions are still unanswered concerning their mechanisms of ionic transport. Differences in the transport mechanisms operating in the ductal epithelium has been described both among different species and in the different regions of the ductal tree. In a review it was summarized the methods developed to study pancreatic duct secretion both in vivo and in vitro, the different mechanisms of ionic transport that have been reported to date in the basolateral and luminal membranes of pancreatic ductal cells and the regulation of pancreatic duct secretion by nervous, endocrine and paracrine influences [129].

Cholecystokinin

Cholecystokinin (CCK)-dependent exocrine pancreatic regulation seems to involve different pathways in different species. The aims in one study were to explore the enteropancreatic reflex in the CCK-mediated regulation of the exocrine pancreas and to evaluate a possible involvement of this reflex in the endocrine insulin release. In anesthetized pigs, CCK-33 in increasing doses (4-130 pmol/kg per 10 min) was infused locally to the gastroduodenal artery, or systemically via the jugular vein. Also, a low CCK-33 dose (13 pmol/kg) was injected to the duodenum/antrum area before and after a bilateral truncal vagotomy. Cholecystokinin-33 in the physiological dose range 4 to 32 pmol/kg per 10 min increased protein and trypsin outputs after local infusion to the antral-duodenal area, whereas it had no effect after systemic infusion. Cholecystokinin-33 in the pharmacological dose range 64 to 130 pmol/kg per 10 min further increased the secretion after both local and systemic infusions. Only CCK-33 infusions in the pharmacological dose range were able to elevate the plasma insulin levels. Vagotomy had no effect on CCK-33-mediated stimulation of the enzyme release, whereas it had a significant effect on the plasma insulin level [130].

Pancreatic function in the elderly

Among the various studies of pancreatic function in the elderly published so far, none have dealt with subjects over 90 years of age. The aim of one study was to examine pancreatic function in healthy individuals over 90 years old. Sixty-eight healthy noninstitutionalized elderly persons, aged 91-104 years, with a mean age of 95 years, and 63 younger controls were studied. Pancreatic function was studied by determining fecal elastase 1 concentration. In addition to this test, it was also measured serum amylase, pancreatic isoamylase and lipase in 53 of the 68 elderly subjects. All but 1 of the 68 elderly subjects had normal elastase 1 values; the one who did not had a value slightly below normal. No significant difference with controls was found. Serum pancreatic enzymes were normal in almost all of the 53 elderly studied; 3 had a mild elevation only of amylase and 1 had a persistent elevation of amylase, pancreatic isoamylase and lipase. It was concluded that in subjects over 90 years of age, exocrine pancreatic function continues to be normal; if an impairment occurs, it is mild and not significant for digestion of food. In addition, serum pancreatic enzymes remain within normal limits in the vast majority of cases [131].

Ethanol metabolism

To determine tissue-specific effects of alcohol on fatty acid synthesis and distribution as related to functional changes in triglyceride transport and membrane formation tissue fatty

acid profile and de novo lipogenesis were determined in adult male Wistar rats after 5 weeks of ethanol feeding using deuterated water and gas chromatography/mass spectrometry. Liver and pancreas fatty acid profiles and new synthesis fractions were compared with those from control rats on an isocaloric diet. Fatty acid ratios in the liver indicated that there was a more than 2-fold accumulation of stearate to that of palmitate, with an apparent decrease in oleate content. On the other hand, in the pancreas, there was a 17 percent decrease in the stearate-to-palmitate ratio, whereas the oleate-to-palmitate ratio was increased by 30 percent. The fractions of deuterium-labeled palmitate and stearate were substantially reduced in the liver and pancreas of the alcohol-treated animals. Deuterium labeling of oleate was reduced in the liver but not in the pancreas, consistent with the oleate/stearate ratios in these tissues. It was concluded that long-term alcohol exposure results in opposite effects on the desaturase activity in the liver and pancreas, limiting fatty acid transport in the liver but promoting the exocrine function of the pancreas [132].

IAPP

The red wine compound resveratrol can effectively inhibit the formation of amyloid polypeptide, IAPP, amyloid that is found in type II diabetes. In vitro inhibition results do not depend on the antioxidant activity of resveratrol. Further, the markedly enhanced cell survival in the presence of resveratrol also indicates that the small oligomeric structures that are observed during beta-sheet formation are not toxic and could be off-pathway assembly produkts [133].

Glucose metabolism

For type 2 diabetes mellitus treatments based on the incretin hormones provide a novel approach to address some components of the complex pathophysiology of type 2 diabetes. The purpose of one review was to elucidate the science of the incretin hormones and describe the incretin effect and its regulatory role in beta-cell function, insulin secretion, and glucose metabolism. The key endogenous hormones of incretin system are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); a key enzymatic regulator of these hormones is dipeptidyl peptidase-4, which rapidly inactivates/degrades the incretin hormones. The roles of the incretin hormones in the regulation of glucose metabolism and other related physiologic processes such as gut motility and food intake are disturbed in type 2 diabetes. These disturbances – defects in the incretin system – contribute to the pathophysiology of type 2 diabetes in manifold ways. Consequently, therapies designed to address impairments to the effects of the incretin hormones have the potential to improve glucose regulation and other abnormalities (e.g. weight gain, loss of beta-cell function) associated with type 2 diabetes [134].

Progressive loss of beta-cell function is a pathophysiologic hallmark of type 2 diabetes. Recent science has elaborated on the role of the incretin hormones on beta-cell function and insulin secretion, as well as the role that incretin-based pharmacotherapies may have on glycemic control and beta-cell function, possibly altering the progressive loss of beta-cell function and possibly reversing/halting disease progression. However, incretin-based therapies may also have benefits extending beyond glycemic control and insulin secretion. In one review it was examined some of those "beyond-glycemic" benefits, including presentation of data on weight reduction, blood pressure lowering, beneficial changes in the lipid profile, and improvements in myocardial and endothelial function [135].

Diabetic overview

To provide an overview of the disease burden and current strategies in the treatment of patients with type 2 diabetes a Medline search of all relevant clinical and review articles was done. The prevalence of diabetes in the United States has reached epidemic proportions with the total diagnosed and undiagnosed cases among people aged 20 years or older estimated at 13 percent, and it continues to rise at an alarming rate. This upsurge has been paralleled by an increase in rates of obesity. Type 2 diabetes accounts for up to 95 percent of diabetes cases and is often comorbid with hypertension and dyslipidemia. It was concluded that tight glycemic control is necessary for the management of type 2 diabetes, but progressive deterioration of beta-cell function can lead to a loss of glycemic control. Oral antidiabetes drugs and insulin are effective but do not always correct the associated metabolic and glucoregulatory dysfunctions, and hypoglycemia and weight gain are common adverse effects of these agents. A clear need exists for aggressive therapeutic options-particularly incretin-based agents-that can be combined with existing agents to preserve beta-cell function and halt the progression of type 2 diabetes [136].

Incretin mimetics

As a consequence of excess abdominal adiposity and genetic predisposition, type 2 diabetes is a progressive disease, often diagnosed after metabolic dysfunction has taken hold of multiple organ systems. Insulin deficiency, insulin resistance and impaired glucose homeostasis resulting from beta-cell dysfunction characterize the disease. Current treatment goals are often unmet due to insufficient treatment modalities. Even when combined, these treatment modalities are frequently limited by safety, tolerability, weight gain, edema and gastrointestinal intolerance. Recently, new therapeutic classes have become available for treatment. A review will examine the new therapeutic classes of incretin mimetics and enhancers in the treatment of type 2 diabetes [137].

A PubMed search was conducted for the years 2000-2009, using as keywords the names of glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide and liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, alogliptin, and saxagliptin). The author included randomized controlled trials of incretin therapies that were published in English and enrolled $\pm$100 participants. A total of 27 randomized controlled studies of incretin therapy were identified and included in the review. GLP-1 receptor agonists and DPP-4 inhibitors were evaluated at different points in the diabetes treatment spectrum, i.e. added to diet and exercise alone (monotherapy) or added to oral antihyperglycemic regimens (combination therapy). In addition to decreasing glycemia in type 2 diabetes, incretin therapies may improve other important parameters, including beta-cell function, blood pressure, and lipid levels, with a low risk for hypoglycemia. A comparison of the study data differentiates the clinical profiles of the GLP-1 receptor agonists, which are associated with weight loss, and DPP-4 inhibitors, which are weight neutral, as well as the individual agents within each class [138].

Type 2 diabetes mellitus has become an enormous and worldwide healthcare problem that is almost certain to worsen. Current therapies, which address glycemia and insulin resistance, have not adequately addressed the complications and treatment failures associated with this disease. New treatments based on the incretin hormones provide a novel approach to address some components of the complex pathophysiology of type 2 diabetes. The purpose of one review was to elucidate the science of the incretin hormones and describe the incretin effect and its regulatory role in beta-cell function, insulin secretion, and glucose metabolism. The key endogenous hormones of incretin system are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); a key enzymatic regulator of these hormones is dipeptidyl peptidase-4, which rapidly inactivates/degrades the incretin

hormones. The roles of the incretin hormones in the regulation of glucose metabolism and other related physiologic processes such as gut motility and food intake are disturbed in type 2 diabetes. These disturbances – defects in the incretin system – contribute to the pathophysiology of type 2 diabetes in manifold ways. Consequently, therapies designed to address impairments to the effects of the incretin hormones have the potential to improve glucose regulation and other abnormalities (e.g. weight gain, loss of beta-cell function) associated with type 2 diabetes [139].

Impaired insulin secretion plays a major role in the pathogenesis of type 2 diabetes mellitus, and progressive loss of beta-cell function is a pathophysiologic hallmark of type 2 diabetes. Recent science has elaborated on the role of the incretin hormones on beta-cell function and insulin secretion, as well as the role that incretin-based pharmacotherapies may have on glycemic control and beta-cell function, possibly altering the progressive loss of beta-cell function and possibly reversing/halting disease progression. However, incretin-based therapies may also have benefits extending beyond glycemic control and insulin secretion. In one review it wasd examine some of those "beyond-glycemic" benefits, including presentation of data on weight reduction, blood pressure lowering, beneficial changes in the lipid profile, and improvements in myocardial and endothelial function [140].

Stem cell therapy

With the already heightened demand placed on organ donation, stem cell therapy has become a tantalizing idea to provide glucose-responsive insulin-producing cells to Type 1 diabetic patients as an alternative to islet transplantation. Multiple groups have developed varied approaches to create a population of cells with the appropriate characteristics. Both adult and embryonic stem cells have received an enormous amount of attention as possible sources of insulin-producing cells. Although adult stem cells lack the pluripotent nature of their embryonic counterparts, they appear to avoid the ethical debate that has centred around the latter. This may limit the eventual application of embryonic stem cells, which have already shown promise in early mouse models. One must also consider the potential of stem cells to form teratomas, a complication which would prove devastating in an immunologically compromised transplant recipient. One review looked at the progress to date in both the adult and embryonic stem cells fields as potential treatments for diabetes. It was also consider some of the limitations of stem cell therapy and the potential complications that may develop with their use [141].

HISTOPATHOLOGY

In type 1 autoimmune diabetes there is a selective destruction of insulin-secreting beta cells. Around the time of clinical presentation, insulitis, a chronic inflammatory infiltrate of the islets affecting primarily insulin containing islets, is present in the majority of cases. The inflammatory infiltrate consists primarily of T lymphocytes; CD8 cells outnumber CD4 cells, there are fewer B lymphocytes and macrophages are relatively scarce. beta cell death may involve the Fas apoptotic pathway since they have been shown to express Fas, infiltrating T lymphocytes express Fas-L and apoptotic beta cells have been described. Hyperexpression of class I MHC by all the endocrine cells in many insulin-containing islets is a well recognized phenomenon, characteristic of the disease. It has been argued that this is an earlier event than insulitis within a given islet and appears to be due to secretion of interferon alpha by beta cells within that islet. A recent study has found evidence of Coxsackie virus infection in beta cells in three out of six pancreases of patients with recent-onset type 1 diabetes. Coxsackie viruses are known to induce interferon alpha secretion by beta cells and this could initiate the sequence of events that culminates in their autoimmune destruktion [142].

Transplanting pancreatic islets

The isolation of islets from the human pancreas critically depends on an efficient enzyme blend. Previous studies have solely focused on the presence of collagenase and neutral protease/thermolysin. Despite improved characterization of these components, the lot-related variability in efficacy still persists suggesting that additional so far disregarded enzymes are required for efficient islet cleavage. Varying activities of a tryptic-like enzyme were now identified within collagenase NB1 lots, which were selected according to a matched ratio between tryptic-like and collagenase activity (TLA-ratio). Rat and human pancreata were processed with current standard procedures. Increasing the TLA-ratio from 1.3 to 10 percent reduced pancreas dissociation time in rats by 50 percent without affecting islet yield, viability, or posttransplant function in diabetic nude mice. Enhancing the TLA-ratio from 1.3 to 12.6 percent for human pancreas processing resulted in a significant reduction of recirculation time and increased incrementally human islet yield without affecting purity, in vitro function or recovery after culture. Optimized pancreas digestion correlated with a higher percentage of islet preparations fulfilling quality criteria for clinical transplantation. It was concluded that TLA is an effective component that should be included in moderate amounts in enzyme blends for human islet isolation to optimize the efficiency and minimize the lot-related variability [143].

Previously, it was found that human islets experimentally transplanted beneath the kidney capsule have lower vascular density than native islets. One study aimed to investigate whether human islets experimentally transplanted into the liver are also poorly revascularized in the same manner as islets at the renal subcapsular site. Human islets were transplanted to nude mice. The vascular density in the intraportally transplanted human islets was found to be similarly low as in human islets transplanted beneath the kidney capsule. The intrahepatic human islets were coated with numerous vessels, but few vessels could be seen within the islets. Human islets transplanted intraportally into the liver become poorly revascularized. This could contribute to the loss of function in human islets transplanted into the liver over time [144].

ACUTE PANCREATITIS

Acute pancreatitis is an inflammatory disease characterized by steady, acute abdominal pain of varying severity, often radiating from the epigastrium to the back. Its presentation ranges from a self-limiting mild disorder to a more severe and fulminant disease. Excessive acinar cell injury leads to a condition called systemic inflammatory response syndrome (SIRS). Protracted SIRS is responsible for most of the life-threatening complications associated with acute pancreatitis. Drugs such as resveratrol and rosiglitazone are being investigated as potential candidates for the treatment of acute pancreatitis [145].

Despite nearly a century of inquiry into the mysteries of the cataclysmic cascade of pancreatic enzyme activation, the key initiating factors and the subsequent mechanisms of glandular damage as well as the varied pathophysiological consequences of acute pancreatic inflammation are still poorly understood. The principal factor that leads to pancreatic injury is believed to be pathological activation of intracellular digestive enzymes, possibly as a result of colocalization of pancreatic zymogens with lysosomal enzymes to produce active trypsin. Disruption of the pancreatic acinar cell membrane is also postulated as a key initiating event in the pathogenesis of acute pancreatitis. Recent work has highlighted the role of disruption of protective mechanisms such as specific trypsin inhibitors (e.g. serine protease inhibitor Kazal type 1), compartmentalization of enzymes, and low intracellular Ca^{2+} concentrations, which prevent pathologic activation of trypsinogen. In addition, the downstream enzymatic, inflammatory, and cell death pathways and the consequent activation of the systemic inflammatory response syndrome in severe acute pancreatitis have received considerable attention, especially with regard to the extrapancreatic facets of the disease. However, contemporary understanding of the pathogenesis is mostly derived from animal models and at the present time, the degree to which these models reflect human disease remains limited [146].

Overall results

To determine overall mortality and timing of death in patients with severe acute pancreatitis and factors affecting mortality a retrospective, observational study of 110 patients admitted to a general intensive care unit (ICU) from 2003 to 2006 was performed. The overall mortality rate was 54 percent (59/110); 25 percent (n=15) of deaths were early ($\leq$ 14 days after ICU admission). There were no significant differences in age, sex, or surgical/medical treatment between survivors and nonsurvivors. Median Acute Physiology and Chronic Health Evaluation (APACHE) II score was significantly higher among nonsurvivors than survivors, and the duration of hospitalization before ICU admission was significantly longer (4 vs 1 day). Among the 59 patients who died, those in the early-mortality group were admitted to the ICU significantly earlier than those in the late-mortality group (3 vs 6.5 days) [147].

Mortality

Mortality in acute pancreatitis has 2 peaks. The first peak is caused by systemic inflammatory response syndrome (SIRS), which takes place in the first week of the disease. Sepsis is responsible for a second peak. It begins 1 to 3 weeks after the onset of acute pancreatitis and is caused by pancreatic superinfection. Sepsis as a result of infected pancreatic necrosis is the most serious complication in late phase of severe acute pancreatitis (SAP) and contributes to the high mortality rate of this disease. This complication is thought to be a result of the bacterial translocation from the gastrointestinal tract. The damage of the microvessels and the subsequent onset of systemic cascade reactions plays also an important role during acute pancreatitis. Recent experimental data suggest also the role of nervous system in etiopathogenesis of acute pancreatitis. It may be assumed that the

diagnostic and treatment strategy can not improve without a thorough knowledge of the physiology and patophysiology of acute pancreatitis [148].

Epidemiology and demography

An increased incidence

The pathophysiology and treatment of acute pancreatitis has been intensely studied during the last century and our aim is to review recent evidence and achievements in the diagnosis and treatment as pancreatitis is a growing problem in Europe, posing significant medical, surgical and financial sequelae. The mean age of the first attack is in the 6th decade which can be explained by an increasing incidence of gallstone pancreatitis among white women over the age of 60 years. The incidence of acute pancreatitis has been reported to be markedly increasing. The explanation of this increased incidence could be explained by the routine testing of pancreatic enzymes in patients presenting with abdominal pain at emergency departments, and in over-diagnosis in cases of non-specific increases in enzymes due to other causes. Another explanation is an increase in the incidence of gallstone disease and obesity in the population [022].

Risk factors in the US

Knowledge of the number of deaths caused by risk factors is needed for health policy and priority setting. The aim of one study was to estimate the mortality effects of the following 12 modifiable dietary, lifestyle, and metabolic risk factors in the United States (US) using consistent and comparable methods: high blood glucose, low-density lipoprotein (LDL) cholesterol, and blood pressure; overweight-obesity; high dietary trans fatty acids and salt; low dietary polyunsaturated fatty acids, omega-3 fatty acids (seafood), and fruits and vegetables; physical inactivity; alcohol use; and tobacco smoking. It was used data on risk factor exposures in the US population from nationally representative health surveys and disease-specific mortality statistics from the National Center for Health Statistics. In 2005, tobacco smoking and high blood pressure were responsible for an estimated 467,000 (95 % confidence interval 436,000 to 500,000) and 395,000 (372,000 to 414,000) deaths, respectively, accounting for about one in five or six deaths in US adults. Overweight-obesity (216,000; 188,000 to 237,000) and physical inactivity (191,000; 164,000 to 222,000) were each responsible for nearly 1 in 10 deaths. High dietary salt (102,000; 97,000 to 107,000), low dietary omega-3 fatty acids (84,000; 72,000 to 96,000), and high dietary trans fatty acids (82,000; 63,000 to 97,000) were the dietary risks with the largest mortality effects. Although 26,000 (23,000 to 40,000) deaths from ischemic heart disease, ischemic stroke, and diabetes were averted by current alcohol use, they were outweighed by 90,000 (88,000 to 94,000) deaths from other cardiovascular diseases, cancers, liver cirrhosis, pancreatitis, alcohol use disorders, road traffic and other injuries, and violence [149].

Germany

Several European studies have reported an increase in acute pancreatitis. Therefore, it was decided to investigate whether acute pancreatitis in one area of Germany also displays changes in frequency, etiology, and severity over time. The study included 608 patients with a first attack of acute pancreatitis, all from Lüneburg County, northern Germany, admitted to one municipal hospital between 1987 and 2006. The age-standardized rate (world) per 100,000 inhabitants/year was 16.0 for men and 10.2 for women. Division of the study period into four 5-year segments revealed no increase or decrease in the frequency of acute pancreatitis nor did the etiology change. The severity of disease, however, decreased over the course of time, as shown by lower Ranson scores, a lower proportion of cases with

necrosis or a severe course, and lower lethality. Other measures of severity remained unchanged. The decrease in severity was particularly marked in patients with alcohol-related pancreatitis who are apparently seeking hospital treatment earlier than used to be the case. It was concluded that in contrast to other European countries (Denmark, United Kingdom, The Netherlands, and Sweden), this study showed no change over time in the frequency or etiology of acute pancreatitis. There were, however, signs of a decrease in disease severity, and this aspect merits further investigation [150].

India

A prospective analysis of the epidemiology and outcome of patients admitted with acute pancreatitis to a tertiary health care centre in Goa, India, was carried out during the time period of 2003 to 2005. The patients studied were those who were admitted to the Goa Medical College with a diagnosis of acute pancreatitis based on a serum amylase of greater than 180 Somogyii units with appropriate clinical and radiographic evidence. The selection criteria were fulfilled by 282 patients. Acute pancreatitis accounted for 2.3 percent of all admissions and 4.9 percent of all deaths in the department of surgery. The disease was seen to affect males more commonly (96 %), alcohol, being the predominant (92 %) aetiological factor. The median age for occurrence of the disease was 40 years. Severe acute pancreatitis was encountered in 33 percent of cases with a mortality rate of 12 percent. Mortality was higher in patients older than 50 years. The widespread availability and use of locally made cheaper varieties of alcohol in the geographical location explains the trend towards alcoholic pancreatitis and younger age groups being affected by the disease [151].

Etiologic factors and factors of importance for development of pancreatitis

Cytokines

TNF

To determine whether increases in soluble tumor necrosis factor receptors (sTNFRs) are associated with the levels of cytokines and proteinases in patients undergoing major surgery. Eleven patients who underwent esophagectomy for squamous cell carcinoma of the thoracic esophagus were studied. The circulating blood concentrations of interleukin-6 (IL-6), IL-8, sTNF-R55, sTNF-R75, elastase/al-proteinase inhibitor complex (elastase) and matrix metalloproteinase-9 (MMP-9) were measured by ELISA or EIA before surgery, just after surgery, and on postoperative days (POD) 1 and 3. The levels of serum IL-6, plasma IL-8, plasma elastase and plasma MMP-9 increased significantly after surgery, peaking just after surgery or on POD 1 and then declining. In contrast, the serum levels of sTNFRs increased approximately 2-fold just after surgery compared with the preoperative values and then remained elevated. The IL-6 level correlated with the levels of sTNF-R55 and sTNF-R75 after surgery. These results suggest that increases of IL-6, serine proteinases and MMPs may be involved in the upregulation of sTNFRs in patients undergoing major surgery [152].

Interleukin 17

The evaluation of the interleukin 17 capacity as precociously predictive marker of the severe forms of acute pancreatitis was done in a prospective and diagnosis study that took place during 2006-2008 on a sample of 83 subjects hospitalized with acute pancreatitis. Among these, 48 have submitted forms mild disease and formed batch A. Subjects with severe acute pancreatitis formed batch B (n=16), to whom it was applied peritoneal lavage extended by laparoscopic method and batch C (n=19), who have used conventional methods of treatment, had their serum concentrations of interleukin 17 determined in the first and tenth days of admission for the subjects of A and C lots and in the first, third and tenth day at then subjects of B lot. Interleukin 17 has proved a sensitivity of 97 percent and a specificity of 94

percent in early identification forms of severe acute pancreatitis, with a correlation coefficient of 0.81. The correlation was good even in combination with organic disfunction (0.66) and the risk of death (0.54). The predictive capacity of sepsis has been reduced (0.44). The dynamics of this cytokines show a significant decrease in concentrations forms mild disease (batch A) and in severe forms treated with peritoneal extended lavage (lot B). In conversely, the subjects treated by conventional methods (lot C) the decrease was not significant between the first and tenth days of admission. A similar dynamic has been recorded after short peritoneal lavage, lasting three days. At large in, the concentrations of interleukin 17 evolved in parallel with those of interleukin 6 [153].

Zinc and copper

The aims of one study were to measure the concentrations of zinc (Zn), copper (Cu), and metallothionein and the Cu/Zn superoxide dismutase activity as elements engaged in an essential manner in the prooxidative and antioxidative balance of organism and to demonstrate the degree to which metallothionein and Cu/Zn superoxide dismutase are involved in the inflammatory processes occurring in the pancreas. The concentration of metallothionein was measured by immunoenzymatic method. Serum Cu/Zn superoxide dismutase activity was determined using a commercial test. The measurements of Zn and Cu concentrations in serum were assessed with the use of flame atomic absorption spectrometry. Lowered serum Zn concentration and higher Cu level were observed in the serum of patients with chronic exacerbated pancreatitis and chronic pancreatitis. The significant increase of metallothionein concentration and Cu/Zn superoxide dismutase activity was observed in the blood of patients with chronic exacerbated pancreatitis and chronic pancreatitis. In slices of the pancreas during pancreatitis, it was observed in immunohistochemical reaction the variable involvement of Cu/Zn superoxide dismutase and metallothionein. The results presented in these studies indicate an essential and variable involvement of antioxidants such Cu/Zn superoxide dismutase and metallothionein and disordered Cu and Zn homeostasis depending on the progression of inflammatory processes in patients with pancreatitis [154].

Propofol

The use of propofol is controversial in patients with a history of acute pancreatitis or those taking drugs, including certain chemotherapeutic drugs that are associated with pancreatitis. To investigate this issue, it was reviewed the medical records of all children who were diagnosed with pancreatitis while receiving chemotherapy for acute leukemia during a 5-year period. A temporal relationship between propofol use and development of acute pancreatitis could not be established. Propofol can thus be considered for general anesthesia in children who are receiving chemotherapeutic drugs that are themselves associated with acute pancreatitis or those who have a history of chemotherapy-induced pancreatitis [155].

Genetic polymorphism

Systemic inflammatory reaction in acute pancreatitis is associated with activation of the coagulation system. The prothrombotic component of the coagulation system, which may promote microvascular thrombosis and vital organ injury, is strengthened by genetic factors such as polymorphism of plasminogen activator inhibitor type 1 (PAI-1) and factor V Leiden (FVL) mutation. It was now studied the occurrence of FVL and PAI-1 4G/5G polymorphisms in patients with acute pancreatitis This case control association study included 397 patients with acute pancreatitis and 310 controls. Severe acute pancreatitis was determined according to the Atlanta Classification. Genotyping was performed by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry-assisted genotyping method. Factor V Leiden was identified in 5 (3.3 %) of 152 cases of severe acute pancreatitis and in 8 (3.3 %)

of 245 cases of mild acute pancreatitis. The prothrombotic PAI-1 4G allele frequency was 0.49 for patients with severe acute pancreatitis and 0.57 for patients with mild acute pancreatitis, which was a significant difference. Patients with septic infectious complications (n=47) and patients with organ failure (n=55) had genotype distribution not different from those with mild, uncomplicated disease (n=245). The results do not support the hypothesis that prothrombotic polymorphisms such as FVL mutation and PAI-1 4G/5G are associated with acute pancreatitis severity [156].

Oxidative stress

Acute pancreatitis is fatal when severe and oxidative stress is postulated to play an important role in its pathophysiology and the development of complications. Patients presenting to a gastroenterology ward with early acute pancreatitis, i.e. within 72 hours of onset of pain, were included in the study. Also samples from 50 healthy controls were obtained for comparison. Oxidative stress was estimated by levels of blood superoxide dismutase (SOD) and lipid peroxidation (thiobarbituric acid reactive substances; TBARS) and antioxidant status (AOS) by the ferric reducing ability of plasma (FRAP) and vitamin C at days 1, 3, and 7 of admission. Oxidative stress was significantly higher in cases as compared with controls on all days and showed a gradual decrease from day 1 to 7. TBARS showed a higher fall in mild acute pancreatitis and better clinical outcome. Regarding the AOS, FRAP was significantly lower in cases and decreased significantly from day 1 to 3. Thus, high oxidative stress was observed during early phase of acute pancreatitis and a gradually improving antioxidant status was associated with a better clinical outcome in patients with acute pancreatitis [157].

Hemoconcentration

It was examined the relationship between early hemoconcentration and in-hospital mortality in an observational cohort study of patients with acute pancreatitis. Data was collected from 177 US hospitals from 2004 to 2005. Early hemoconcentration was defined as hemoglobin > 14.6 mg/dl (hematocrit ~44 %) at any point during the first 24 hours of initial hospitalization. For transferred cases, it was linked clinical data from the first hospitalization to outcomes from the second hospitalization. It was then examined the impact of hospital transfer status on the prognostic utility of hemoconcentration. It was identified 388 (2.2 %) cases as interhospital transfers. Of these, it was successfully linked 198 (51 %) to their initial hospitalization. Early hemoconcentration was associated with increased mortality among transferred cases (odds ratio 7.4, 95 % confidence interval 1.6 to 35.4). However, no such relationship existed among non-transferred cases (odds artio 0.9, 95 % confidence interval 0.7 to 1.2). Differences in outcome between transferred versus nontransferred cases were not explained by extent of comorbid illness or initial disease severity (either APACHE II or organ failure). It was concluded that early hemoconcentration predicted increased risk of mortality only among transferred cases despite similar levels of initial disease severity [158].

Caboxypeptidase B

The concentration of carboxypeptidase B activation peptide (CAPAP) is proposed to be a predictor of severe acute pancreatitis. The activated protein C (APC)-protein C inhibitor (PCI; APC-PCI) complex in plasma could be useful in detecting the hypercoagulative condition in severe acute pancreatitis. In a prospective study, mild (n = 50) and severe (n = 9) cases of acute pancreatitis were compared with respect to levels of CAPAP and APC-PCI, and sorted in time intervals from onset of symptoms to sampling. The peak values of the C-reactive protein (CRP) within the 1st week were also compared. CRP detected the severe cases with a sensitivity of 0.89 and a specificity of 0.74 (cut-off level 200 mg/l). In the interval 0-72 h, CAPAP could predict the severity of the disease in serum and urine (sensitivity 0.52/0.29,

specificity 0.73/0.93, cut-off 2 nM/60 nM). The level of APC-PCI in plasma could predict the severe condition in the interval 0-24 h after the onset of symptoms (sensitivity 0.6, specificity 0.66, cut-off level 0.54 μg/l). It was concluded that off the parameters explored, CRP is still the best biochemical marker to distinguish between severe and mild acute pancreatitis. CAPAP could be useful in combination with other tests, but the APC-PCI complex's diagnostic time interval is too short to be used in the clinical routine [159].

Obesity

Obesity markedly increases the risk of severe acute pancreatitis (SAP), possibly through the action of adipokines. It was tested the hypothesis that serum adiponectin, the primary anti-inflammatory adipokine, is associated with functional polymorphisms in the adiponectin gene (ADIPOQ) and inversely associated with SAP. Severe AP was defined as the presence of remote organ failure. ADIPOQ polymorphisms rs2241766T>G and rs1501299G>T were evaluated by DNA sequencing. Serum samples were assayed using a Luminex assay. One hundred thirty-three patients with acute pancreatitis and 94 healthy controls were ascertained. Adiponectin levels were measured in 60 patients with early serum samples (27 patients with mild AP and 33 patients with SAP). Adiponectin levels from days 1 to 3 were inversely correlated with body mass index (BMI) and were significantly lower for patients with SAP than those with mild acute pancreatis. Neither ADIPOQ polymorphism affected susceptibility to or severity of acute pancreatitis. A receiver operating characteristics curve using adiponectin levels as the severity predictor provided an area under the curve of 0.75. Serum adiponectin levels in patients with acute pancreatitis are inversely correlated with BMI and organ dysfunction [160].

Dyslipedemia

Admissions with acute pancreatitis were prospectively evaluated. A comparison of the demographic profile, etiology, disease severity scores, complications and deaths was made in relationship to the lipid profiles. From 2001 to 2005, there were 230 admissions. The pancreatitis was associated with alcohol (63 %), gallstones (18 %), idiopathic (9 %) and isolated dyslipidaemia (10 %). Dyslipidaemia was significantly different between the two predominant race groups: Indian 51 percent and African 18 percent. Seventy-eight (34 %) had associated dyslipidemia and 152 (66 %) were normolipaemic at admission. The average body mass index was significantly higher in the dyslipidemic group (27 ± 6) than in the normolipemic group (24.5 ± 6.20). The mortality rate was similar between the dyslipidemic and normolipemic patients (10 and 8 %, respectively) and unrelated to race. The 9 deaths in the dyslipidaemic group occurred in those with persistent hypertriglyceridaemia irrespective of its level. It was concluded that adverse outcomes in those with dyslipidaemia were predominantly associated with hypertriglyceridaemia [161].

Dominant dorsal duct syndrome

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 two patients are 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 one 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 sphinctero-

plasty 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 [162].

Classification and prediction of severity

The prediction of severe acute pancreatitis should be achieved by careful ongoing clinical assessment coupled with the use of a multiple factor scoring system and imaging studies. Over the past 30 years several scoring systems have been developed to predict the severity of acute pancreatitis. However, there are no complete scoring index with high sensitivity and specificity till now. The interest in new biological markers and predictive models for identifying severe acute pancreatitis testifies to the continued clinical importance of early severity prediction. Among them, IL-6, IL-10, procalcitonin, and trypsinogen activation peptide are most likely to be used in clinical practice as predictors of severity. Even if contrast-enhanced CT has been considered the gold standard for diagnosing pancreatic necrosis, early scanning for the prediction of severity is limited because the full extent of pancreatic necrosis may not develop within the first 48 hour of presentation [163].

Scoring systems

In acute pancreatitis early identification of high-risk patients can be difficult. For this reason, a plethora of different prognostic variables and scoring systems have been assessed to see if they can reliably predict the severity of pancreatitis and/or subsequent mortality. All studies that focused on acute pancreatitis, including retrospective series and prospective trials, were retrieved and analysed for factors that could influence mortality. Articles that analysed factors influencing the severity of the disease or the manifestation of disease-related complications were excluded. Fifty-eight articles meeting the inclusion criteria were identified. Among the various factors investigated, APACHE II seemed to have the highest positive predictive value (69 %). However, most prognostic variables and scores showed high negative predictive values but suboptimal values for positive predictive power. It was concluded that despite the proliferation of scoring systems for grading acute pancreatitis, none are ideal for the prediction of mortality. With the exception of the APACHE II, the other scores and indexes do not have a high degree of sensitivity, specificity and predictive values [164].

The distinction between mild and severe forms of acute pancreatitis within 24-48 hours of hospital admission is very important for the treatment of these patients. The usage of multifactorial scoring systems holds a lot of promise, reaching reliability in the disease severity estimation of approximately 70-80 percent. The main purpose of one prospective study was to assess the correlation of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Bernard Organ Failure Score (BOFS) scoring systems in estimation of disease severity and outcome prediction. Sixty patients with acute pancreatitis participated in the study, all of them scored with the APACHE II and BOFS scores. The results were used for integration of laboratory and clinical parameters. In the study, it was found a highly significant correlation between the APACHE II and BOFS scores from the disease onset until the end of treatment.There was a highly significant correlation between these two scores and the serum C-reactive protein concentration level. The concept of the BOFS score has more advantages than the APACHE II score in the patients with severe forms of acute pancreatitis with organ dysfunction [165].

Single factors

Renal rim grade

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 (CT) 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 APACHE II score, using a receiver operating characteristic analysis. The exacerbation rates into severe disease were 3 percent (grade 1), 48 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 was comparable with other scoring systems. It was concluded that renal rim grade is useful for the evaluation of the severity of AP [166].

Organ failure

Organ failure (OF) is a main cause of death in severe acute pancreatitis (SAP). One study had the primary aim to evaluate the morbidity and mortality of patients admitted with SAP with no OF (NOF), single OF (SOF), and multiple ($\geq$2) OF (MOF). Medical records of 207 consecutive patients admitted with SAP to the Mayo Clinic between 1992 and 2001 were reviewed. OF was defined according to the Atlanta classification and patients were categorized in the three groups: NOF, SOF, and MOF. Primary outcomes were in-hospital mortality, duration of hospitalization, need for the intensive care unit (ICU), and the mean length of stay in the ICU. Organ failure occurred in 108 patients (52 %). Gastrointestinal bleeding occurred in 18 percent, respiratory failure in 36 percent, hypotension in 28 percent, and renal failure in 26 percent. Compared to patients with MOF, patients with NOF had significantly shorter hospitalizations (28 vs 55 days), less need for ICU care (50 % vs 90 %), shorter time in the ICU (5 vs 34 days), and decreased in-hospital mortality (2 % vs 46 %). Odds ratios evaluating the risk of in-hospital mortality for subjects with any organ failure was 28 (7-186), 10 (2-69) for patients with SOF, and 64 (15-464) for patients with MOF. It was concluded that patients with SAP and NOF have prolonged hospitalizations but low mortality. The Atlanta classification should be revised to include a patient group defined as "moderately severe acute pancreatitis" that identifies those patients currently classified as SAP without organ failure [167].

Albumin

Several studies indicated that the mortality rate of patients with acute pancreatitis is currently approximately 3.8 to 7.0 percent, in severe acute pancreatitis (SAP), it varies from 7 to 42 percent. In previous studies, several biological markers and clinical events had been used to predict the mortality. However, few studies have addressed the role of factors as independent predictors that can early predict fatal outcome in hospitalized medical patients. 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 SAP, particularly the effect of C-reactive protein (CRP), albumin (ALB), and total cholesterol (TC). The mean age of the 338 patients with SAP was 54 years. The overall inhospital mortality rate was 8.3 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 total colesterol level between 4.37 to 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. Subanalysis indicated that CRP was negatively linearly associated with TC. This analysis also identified that the odds ratio of hypoalbuminemia for mortality was much higher than that of high CRP levels. The ability of elevated serum TC level to predict survival in SAP seems unintuitive because the primary cause of acute pancreatitis is hypercholesteremia, which is a strong risk factor to SAP. Moderately elevated TC levels can increase resistance to inflammatory reaction and reduce the severity of SAP and the rate of mortality [168].

Adiponectin

Obesity markedly increases the risk of severe acute pancreatitis, possibly through the action of adipokines. It was tested the hypothesis that serum adiponectin, the primary anti-inflammatory adipokine, is associated with functional polymorphisms in the adiponectin gene (ADIPOQ) and inversely associated with severe acute pancreatitis, defined as the presence of remote organ failure. ADIPOQ polymorphisms rs2241766T>G and rs1501299G>T were evaluated by DNA sequencing. One hundred thirty-three patients with acute pancreatitis and 94 healthy controls were ascertained. Adiponectin levels were measured in 60 patients with early serum samples (27 patients with mild AP and 33 patients with SAP). Adiponectin levels from days 1 to 3 were inversely correlated with body mass index (BMI) and were significantly lower for patients with SAP than those with mild AP. Neither ADIPOQ polymorphism affected susceptibility to or severity of acute pancreatitis. A receiver operating characteristics curve using adiponectin levels as the severity predictor provided an area under the curve of 0.75. Serum adiponectin levels in patients with acute pancreatitis are inversely correlated with BMI and organ dysfunction. Further studies are needed to determine whether adiponectin is a marker of low BMI or if it provides significant protection from SAP [169].

Soluble form of the receptor for advanced glycation end products (sRAGE)

To study in patients with acute pancreatitis the plasma soluble form of the receptor for advanced glycation end products (sRAGE) and high-mobility group box chromosomal protein 1 (HMGB1) levels, followed-up for 12 days after hospitalization, in relation to the occurrence of organ failure and mortality. It was studied 38 patients with severe acute pancreatitis and organ failure (grade 2) and a control group (127 patients) consisting of 38 patients with severe acute pancreatitis without organ failure (grade 1) and 89 patients with mild acute pancreatitis (grade 0). Plasma samples for determination of HMGB1 and sRAGE levels were collected on admission and on days 1 and 2, days 3 and 4, and days 7 and 12 after admission. The median of the highest sRAGE levels was higher in grade 2 patients than in grade 0 plus grade 1 patients. Among the patients with detectable HMGB1, the median of the highest HMGB1 levels was 117 ng/mL in grade 2 patients and 87 ng/mL in grade 0 plus grade 1 patients. It was thus demonstrated that sRAGE level, but not HMGB1 level, is significantly higher in acute pancreatitis patients who develop organ failure than in acute pancreatitis patients without organ failure who recover [170].

High- versus low-volume hospitals

Acute pancreatitis

Although limited initially to operative procedures, studies evaluating the relationship between hospital volume and outcome have been extended to include medical conditions such as myocardial infarction and critical care. In an analysis of the Nationwide Inpatient Sample, a study evaluated the impact of treatment in a high volume center on in-hospital mortality, length of stay, and hospital charges in acute pancreatitis. High-volume centers were defined as the top one third of hospitals by the number of acute pancreatitis admissions in each survey year. The main finding was that adjusted mortality, length of stay, and hospital charges were reduced when high-volume centers were compared with low-volume centers.

An inherent difficulty in comparing outcomes across hospitals is the difference in baseline clinical severity of diseases. High-volume centers typically serve as referral hospitals and are likely to treat a more severely ill patient population. As a result, high-volume centers that accept outside hospital transfers may report worse overall outcomes compared with low-volume centers. The use of propensity scores to create a matched cohort of patients has emerged as an important method for risk adjustment in outcomes research. A characteristic feature of a propensity-matched cohort study is that patients are matched according to exposure, in contrast to a traditional case-control study wherein patients are matched according to outcome. After risk adjustment, treatment in a high-volume center was then associated with reduced mortality, length of stay, and charges. There are several potential explanations for the impact of hospital volume on outcomes in acute pancreatitis. In the past decade, numerous developments have emerged in management of acute pancreatitis, including aggressive fluid resuscitation, enteral nutritional support, and use of innovative endoscopic, radiologic, and operative techniques for specific complications. The management of complicated cases of acute pancreatitis requires not only the availability of numerous specialty services (critical care, gastroenterology, surgery, and interventional radiology), but also the experience to coordinate such multidisciplinary care. The task at hand is to identify which practices contribute to the success of high-volume centers as well as to determine which patients may benefit from treatment in a high-volume center. The impact of hospital volume on outcomes in acute pancreatitis requires further evaluation before policy decisions can be considered [171].

Cholecystectomy

It was explored whether admission volumes for cholecystectomy and pancreatitis were associated with receiving cholecystectomy after hospitalization for acute biliary pancreatitis (ABP). It was identified admissions for ABP in the Nationwide Inpatient Sample between 1998 and 2003. It was 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 ABP was 50 percent. After adjustment for confounders, the likelihood of cholecystectomy increased with every quartile of cholecystectomy 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, vs bottom quartile). Admissions to hospitals in the top quartile for ERCP volume (>35 ERCPs/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. It was concluded US hospitals are not achieving targets for cholecystectomy after acute biliary pancreatitis as set by national and international guidelines. Centers with smaller cholecystectomy volumes are the least adherent to recommendations for cholecystectomy possibly because of hospital-level resource limitations [172].

Diagnostics in acute pancreatitis

Symptoms

It was reported the coexistence of Cullen's and Grey Turner's signs in acute pancreatitis [173].

Urinary trypsinogen-2

There is not any quantitative diagnostic test for acute pancreatitis. In the present study it was investigated the value of the qualitative urinary trypsinogen-2 measurement in the diagnosis of acute pancreatitis by an immuno-chromatographic dipstick test. A prospective, randomized, clinical trial was planned on 99 patients (53 male, 46 female; male/female : 1.11; age range: 16-83; mean age: 37.4). Patients were divided into two groups: 50 cases were referred to our emergency surgical unit due to abdominal pain and diagnosed with acute pancreatitis by abdominal computerized tomography (CT) (group 1); 49 cases were referred to the emergency surgical unit due to abdominal pain and whose abdominal CTs did not show any sign of acute pancreatitis (group 2). Qualitative urinary trypsinogen-2 measurement, abdominal CT and blood amylase values were obtained in all cases. In group 1, urinary trypsinogen-2 measurement was found positive in 28 cases out of 50 cases diagnosed with acute pancreatitis (56 % sensitivity). In group 2, results were found positive in 3 out of 49 patients with abdominal pain, who lacked an acute pancreatitis diagnosis (91 % specificity). Severe intra-abdominal inflammation was present in three cases of group 2 where we obtained false positive results which may stimulate the pancreatic exocrine sekretion [174].

Dip-slide diagnosis

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 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 acute 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 87 percent (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 %). It was concluded that UTDT 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 [175].

Hyperamylasemia

It was reported a case of suspected acute pancreatitis after bilateral total knee arthroplasty. Airway management including jaw thrust maneuvers was performed. Postoperatively, the patient complained of nausea with vomiting. Further examination revealed high serum amylase levels, and an abdominal CT scan revealed confined inflammation near the head of the pancreas. The amylase isozyme patterns identified the salivary-type amylase. A gastroduodenoscopy procedure performed on the 21st postoperative day revealed a duodenal ulcer. It was speculated that the primary cause of hyperamylasemia was accumulation of amylase in the parotid glands and the CT findings showed the inflammation of the pancreas itself or extrapancreatic exudates resulting from duodenal ulcer [176].

Hyperamylasemia is often reported in patients with acute liver failure (ALF). Direct toxic effects of acetaminophen on the pancreas have been postulated, but the occurrence of hyperamylasemia in other etiologies raises the question of whether multiorgan failure is part of the pathogenesis of in this setting. Patients enrolled in the Acute Liver Failure Study Group registry with an admission amylase value available were included. For the purpose of this analysis, hyperamylasemia was defined as $\geq$ 3x upper limits of normal. Patients were

classified as having acetaminophen (APAP)- or non-APAP-induced ALF, and by amylase group: normal (<115), mildly elevated (115-345), or hyperamylasemia (>345). In total, 622 eligible patients were identified in the database, including 287 (46 %) with APAP-induced ALF; 76 (12 %) patients met the criteria for hyperamylasemia. Among patients with hyperamylasemia, 7 (9 %) had documented clinical pancreatitis. The incidence of hyperamylasemia was similar among APAP (13 %) and non-APAP (12 %) patients. Although hyperamylasemia was associated with renal failure and greater Model for End-stage Liver Disease scores for both groups, hyperamylasemia was not an independent predictor of mortality in multivariate analysis. It was concluded that although not an independent predictor of mortality, hyperamylasemia in ALF was present in all etiologies and was associated with diminished overall survival. Hyperamylasemia appeared to be related to renal dysfunction in both groups and multiorgan failure in non-APAP ALF [177].

Asymptomatic

From 2005 to 2008, 63 subjects with asymptomatic pancreatic hyperenzymemia were studied by MRCP. In addition, amylase, pancreatic isoamylase, and lipase were determined for 5 consecutive days. In most subjects (91 %), MRCP showed a normal pancreas. In the remaining 6 subjects (10 %), the following alterations were found: pancreas divisum in 2, small intrapancreatic cyst in 2, anatomic variant of the Wirsung in 1, and mild dilatation of 3 secondary ducts in 1. In these 6 subjects, hyperenzymemia was highly variable from day to day, with frequent normalizations, as was also true for the 30 subjects with no MRCP alterations in whom diurnal enzyme determinations were made. It was concluded that most of the subjects with asymptomatic pancreatic hyperenzymemia did not have pancreatic lesions detectable by MRCP. In the few subjects in whom a lesion was found, the great variability and the frequent transient normalization of serum enzyme levels tend to exclude a relation between the lesion and the hyperenzymemia [178].

In critical ill patients

Elevations in the levels of pancreatic enzymes are observed in up to 80 percent of intensive care patients. Most of these patients do not develop clinically relevant pancreatitis. However, elevations in enzyme levels do represent pancreatic damage with a risk of complications. Different factors have been discussed, which may contribute to pancreatic damage in critically ill patients. These include splanchnic hypoperfusion during shock or major surgery, bacterial translocation, elevated triglyceride levels, development of biliary sluge, and biliary pancreatitis, as well as several drugs. Imaging procedures and inflammatory markers help to identify relevant disease. Several therapeutic options have been discussed recently with a focus on early enteral nutrition. Thus, pancreatic damage is frequently observed in critically ill patients, but in most of these patients, this is without major clinical consequences. However, some patients develop relevant pancreatitis, which contributes to morbidity and mortality [179].

After propofol

Various case reports have indicated a possible relationship between propofol and pancreatitis. However, it is not clear whether this relationship (if any) is dose-related or idiosyncratic. Therefore, a prospective study was conducted to evaluate the effect of different doses of propofol on postoperative pancreatic enzymes and serum triglyceride levels. One hundred and fifty patients, aged 18 to 60 years, belonging to ASA physical status I and II, undergoing non-abdominal surgery were divided into three groups. Anaesthesia was induced with propofol 2 to 2.5 mg/kg in all groups. It was maintained with isoflurane in group I, propofol infusion < 5 mg/kg/h in group II and propofol infusion $\geq$ 5 mg/kg/h in group III. All three groups also received nitrous oxide in oxygen for maintenance of anaesthesia. Serum amylase, lipase and triglyceride were estimated before propofol administration and at 24 and 72 hours postoperatively. The mean values of serum amylase, lipase and triglyceride remained within the normal range in the three groups. These values did not differ significantly in between the groups even despite the significantly different doses of propofol in the three

groups. None of the patients in the three groups developed any feature suggestive of acute pancreatitis in the postoperative period. These findings indicate that propofol administration at recommended doses does not produce dose-related increases in pancreatic enzyme and triglyceride levels in ASA physical status I and II patients [180].

In smokers

The newest conducted investigations showed the significant role of tobacco smoking in inducing pathological changes in pancreas. Additionally exposure to heavy metals presents on polluted environment influences on function this organ. However, the mechanism of development of these changes has not been fully recognised. The aim of this study is to prove the influence of tobacco smoking on total amylase and termolabile amylase activity in serum of smoking and nonsmoking healthy persons and workers at cooper foundry in Legnica occupationally exposed to heavy metals: cadmium, arsenic, lead. Blood has been collected from 28 healthy persons and 60 founders. The enzyme total activity has been determined using the colorimetric method with substrate 1,2-odilauryl-rac-glycero-3-glutaric acid-(6-methylresorufin) ester. The thermolability activity has been determined using the thermolability test. It has been noted significant higher total amylase and thermolabile amylase activity in serum of smoking healthy persons and of non-smoking and smoking founders comparison with non-smoking healthy persons. It hasn't been found significant differences in total and thermolabile amylase activity in smoking founders and non-smoking founders. The fact that there are significant differences in serum amylase activity in serum of smoking and nonsmoking founders in comparison with nonsmoking healthy persons prove a significant influence of exposure to heavy metals on exocrine function of pancreas [181].

Hyperlipedemia

The association of pregnancy, hypertriglyceridemia, and acute pancreatitis is well established even though gestational hyperlipidemic pancreatitis is an uncommon but serious disorder. In women having type I, IV, or V hyperlipoproteinemia (HLP), the superimposition of the physiologic hyperlipidemia of pregnancy may lead to acute pancreatitis. Type III HLP is an inborn error of metabolism characterized by defective apo E, which is a ligand for the receptor-mediated uptake of chylomicron and VLDL remnants by the liver. More than 90 percent of type III HLP subjects are homozygous carriers of apo E2 (Arg158 -> Cys), which displays less than 1 percent binding affinity for the cell surface lipoprotein receptors. However, less than 10 percent of apo E2/E2 homozygous subjects have hyperlipidemia. These observations indicate that other genetic environmental factors or concomitant diseases are necessary for expression of the hyperlipidemia in apo E2/E2 subjects. A case described was the first case of apo E2/E2 homozygous familial type III HLP-related gestational hyperlipidemic pancreatitis. A 39-year-old gravida 3-para woman without known medical history except hyperlipidemia for 3 years and regular medication until 6 months before preparation of gestation was referred to our hospital for acute pancreatitis at 14 weeks of gestation. On arrival, the lipid profiles showed hypercholesterolemia (807 mg/dL) and hypertriglyceridemia (3596 mg/dL). During her stay in the hospital, she received total parenteral nutrition for 14 days and resumed oral intake with low-fat diet smoothly. She was discharged at 18 weeks of gestation and continued with the low-fat diet with fish oil supplement (4 g/d) according to the dietitian's instruction. She gave birth to a healthy male infant at 39 weeks of gestation, and her triglyceride level fell below 1000 mg/dL after delivery. Fish oil is well known to decrease VLDL secretion from the liver and thus lower the production of intermediate-density lipoproteins and low-density lipoprotein. A dose of 3 to 4 g n-3 fatty acids per day decreases serum triglyceride levels by around 30-50 percent in hypertriglyceridemic patients. Thus, fish oil supplement could be an effective therapy for prevention of gestational hyperlipidemic pancreatitis [182].

In a patient with diabetic ketoacidosis complicated by severe elevation of plasma triglyceride

concentrations, treatment with low-level intravenous unfractionated heparin led to prompt reduction in plasma triglyceride concentration and may have prevented the development of hypertriglyceridemia-associated acute pancreatitis. One article reviewed the rationale for this treatment and surveys prior publications using heparin in this and similar settings [183].

d-Dimer

Studies on the clinical value of parameters of hemostasis in predicting pancreatitis-associated complications are still scarce. The aim of one prospective study was to identify the useful hemostatic markers for accurate determination of the subsequent development of organ failure during the very early course of acute pancreatitis. In 91 consecutive primarily admitted patients with acute pancreatitis, prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III, protein C, plasminogen activator inhibitor 1, d-dimer, and plasminogen were measured in plasma within the first 24 hours of admission and 24 hours thereafter. Two study groups comprising 24 patients with organ failure and 67 patients without organ failure were compared. Levels of prothrombin time, fibrinogen, and d-dimer on admission were significantly different between the organ failure and non-organ failure groups, and all these parameters plus antithrombin III were significantly different 24 hours later. d-Dimer in predicting the development of organ failure had a sensitivity, specificity, and positive and negative predictive values of 90, 89, 75, and 96 percent, respectively [184].

CT

A prospective study aimed at evaluating dynamic computed tomography (CT) as a prognostic indicator of local complications in patients with pancreatic necrosis. It was analyzed the relationship between the anatomic pattern of pancreatic necrosis at dynamic CT (pancreatic necrosis, peripancreatic necrosis, and transparenchymal necrosis) and the development of local complications (infected pancreatic necrosis and pseudocyst). One hundred thirty-eight patients were included in the study. Nine patients were excluded, and 86 required surgery. Average time from the onset of symptoms to dynamic CT was 8.3 days. Multivariate analysis identified prognostic factors for local complications:

- extent of pancreatic necrosis (odds ratio, 7)
- presence of peripancreatic necrosis (odds ratio 37)
- transparenchymal necrosis with upstream viable (enhancing) pancreas (odds ratio 36)
- no peripancreatic necrosis (odds ratio 0.016)

It was concluded that dynamic CT prognostic factors useful to predict local complications in patients with pancreatic necrosis were the extent of pancreatic necrosis, presence of peripancreatic necrosis, and the finding of transparenchymal necrosis with upstream viable (enhancing) pancreas [185].

MR

Diffusion-weighted imaging (DWI) is a new magnetic resonance imaging (MRI) technique that evaluates the random motion of water molecules in biological tissues. The clinical utility of DWI has been established for acute stroke and brain tumors. Recent technical advancements in MRI have enabled DWI for the body and several studies have revealed the efficacy of DWI for detecting various diseases. One study documented the efficacy of DWI for the evaluation of acute pancreatitis. MRI was performed with sequences including T1-weighted, T2-weighted, diffusion-weighted imaging, MR cholangiopancreatography (MRCP) and computed tomography (CT) examinations on 11 patients with mild acute pancreatitis. MRI examinations were performed using 1.5-T imager. Two experienced radiologists

evaluated the presence or absence of acute pancreatitis, complications and the cause of acute pancreatitis on the MRI and CT images. There were no differences between the DWI and the CT images regarding their abilities to detect acute pancreatitis. However, DWI could detect acute pancreatitis more clearly than CT without enhancing material. The DWI findings were consistent with the clinical findings, the results of chemical analyses and the CT findings. Furthermore, DWI could detect pancreatic cancer causing acute pancreatitis and MR cholangiopancreatography (MRCP) could detect choledocholithiasis and pancreas divisum causing acute pancreatitis [186].

To determine the diagnostic value of magnetic resonance (MR) grading focusing on elevated signal on T1-weighted images in the prediction of severity and prognosis of acute pancreatitis as compared with the Balthazar computed tomography (CT) grading 31 patients with acute pancreatitis who underwent CT and MR imaging including fat-suppressed T1-weighted images within a 48-hour interval were included in a study. The severity of pancreatitis was evaluated by two observers using the Balthazar CT grading system and an MR grading system that is focused on an elevated signal on T1-weighted images. The MR grading was correlated with the CT grading, and each MR or CT grade was compared with patient outcome parameters, including the duration of hospitalization, local and systemic complications, and clinical outcome grading. There was a significant correlation between CT and MR gradings for pancreatic or peripancreatic inflammation. However, for all of the outcome parameters and outcome grading, a stronger correlation was seen with the MR grading than with the CT grading. No significant correlation was found between CT grading and infected necrosis. It was concluded that magnetic resonance imaging including fat-suppressed T1-weighted images is more accurate to predict the severity and prognosis of acute pancreatitis in comparison with CT [187].

Economical aspects

Both endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) are commonly performed in the evaluation of idiopathic pancreatitis. However, comparative trials of these modalities are lacking, and thus the ideal endoscopic diagnostic strategy to evaluate idiopathic pancreatitis remains unknown. A decision analysis model of patients with 2 attacks of idiopathic pancreatitis with gallbladder in situ was constructed using TreeAge software. It was analyzed cost and overall diagnostic ability of 3 strategies, namely, EUS, ERCP with manometry and bile aspiration, and laparoscopic cholecystectomy. Using the base case analysis, initial EUS was the preferred initial modality for the diagnosis. The expected cost for initial EUS was USD 4469 compared with USD 4615 for ERCP and USD 6268 for laparoscopic cholecystectomy. For cholecystectomy to be the preferred strategy, the total cost would need to be less than USD 1314, well below any realistic cost estimate. If the prevalence of microlithiasis/sludge was greater than 80 percent, then cholecystectomy would be preferred, whereas ERCP would be preferred with a prevalence of less than 41 percent. This cost minimization study identifies EUS as the least costly initial test for the diagnostic evaluation of patients with idiopathic pancreatitis with gallbladder in situ [188].

Differential diagnosis

Ectopic pregnancy may lead to massive haemorrhage, infertility or death. Prompt diagnosis and treatment are crucial to save patients who would otherwise die. Serum amylase and lipase measurements are known biochemical markers of pancreatic inflammation and a recognized finding that may help diagnose acute pancreatitis. It was now reported that a misdiagnosed ruptured ectopic pregnancy in the event of elevated activities of pancreatic enzymes may lead to delayed diagnosis of haemorrhage to peritoneum, resulting in

hemodynamic instability [189].

Acute pancreatitis in children

Epidemiology

Studies show an increased incidence of adult acute pancreatitis in recent decades. A retrospective review of computerized databases at the Children's Hospital of Pittsburgh from 1993 to 2004 was performed. 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 acute 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 acute pancreatitis admissions. It was concluded that the increased incidence of AP at the Children's Hospital of Pittsburgh from 1993 to 2004 may have been primarily driven by increased testing for the disease [190].

Acute pancreatitis in pediatric acute lymphoblastic leukemia

Acute pancreatitis is a complication in children with acute lymphoblastic leukemia (ALL) receiving chemotherapy and has often been reported associated with L-asparaginase (L-asp) therapy. To determine the incidence, risk factors, clinical data, outcome, and mortality of acute pancreatitis in children with ALL a retrospective cohort study was conducted by reviewing the data of total 192 pediatric ALL patients from one hospital from 2000 to 2006 to assess incidence, clinical data, outcome, and mortality of AP. Then, a nested case-control study was conducted to identify potential risk factors for AP by recruiting all patients with acute pancreatitis as cases (n=16), and randomly selected patients without acute pancreatitis to serve as controls up to approximately four controls per case with the total of 68 controls. The total incidence of acute pancreatitis in children with ALL and L-asp-associated acute pancreatitis was 8.3 percent and 7.3 percent, respectively. In patients with L-asp-associated disease, pancreatitis developed after the median 6 doses (range: 1 to 20 doses) of L-asp therapy and the median interval from the last dose of L-asp to the onset of acute pancreatitis was 4 days (range: 1 to 13 days). The mortality rate of the pancreatitis group was significantly higher than the patients without acute pancreatitis (44 % vs 19 %). Mortality was associated with concurrent systemic infection and complications of underlying diseases. Multivariate analysis identified using a high-risk chemotherapy regimen was the only risk factor for acute pancreatitis [191].

Specific injuries

Pulmonary injury

One of the most common complications of acute pancreatitis is acute lung injury, during which intercellular adhesion molecule-1 (ICAM-1) plays an important role by participating in leukocyte adhesion and activation as well as by inducing the "cascade effect" of inflammatory mediators, pulmonary microcirculation dysfunction and even acute respiratory distress syndrome, multiple organ failure or death. Although it is generally believed that the modulatory mechanism of ICAM-1 during this process is associated with the activation of nuclear transcription factor kappa B which is mediated by IL-1, IL-6, IL-18 and oxygen free

radical, etc, further studies are still required to clarify it. Since the upregulation of ICAM-1 expression in the lung during acute lung injury is one of main pathogeneses, the early detection of the ICAM-1 expression level may contribute to the prevention and treatment of acute lung injury. Moreover, reducing pulmonary ICAM-1 expression levels through treatment with anti-ICAM-1 monoclonal antibody (aICAM-1) and antagonists of the neurokinin 1 receptor, etc, should have a positive effect on protecting the lungs during acute pancreatitis. One review aimed to further clarify the relationship between ICAM-1 and acute pancreatitis complicated by acute lung injury, and therefore provides a theoretical basis for the formulation of corresponding therapeutic measures in clinical practice for acute pancreatitis [192].

Osteonecrosis

There was a case report on multifocal osteonecrosis caused by traumatic pancreatitis in a child [193].

Abdominal aortic aneurysm following acute pancreatitis

Vascular lesions may complicate the course of acute pancreatitis. The activated pancreatic enzymes, particularly elastase, might cause lysis of the elastic component of the arterial wall thus leading to aneurysmal changes. It was reported on a case of aneurysm of the infrarenal aorta following complicated acute pancreatitis and treated by endovascular technique [194].

Colonic obstruction in acute pancreatitis

Several forms of colonic complications are rarely observed during the clinical course of acute pancreatitis, and potentially fatal in some cases. Colonic lesions associated with acute pancreatitis can be divided into several groups from a pathogenic point of view. Possible pathogenesis includes: 1) spread of pancreatic enzymes through the retroperitoneum to mesocolon, causing pericolitis, 2) external inflammatory compression by mesocolic mass secondary to necrosis of fatty tissue, and 3) hypotension due to shock, and thrombosis of mesenteric arteries. These might lead to colonic infarction, fistula formation, perforation, and obstruction during follow-up. It was reported two cases of colonic obstruction following acute pancreatitis with possible different mechanisms and review Korean cases. One patient developed colonic obstruction due to severe necrotizing pancreatitis, possibly as a result of pericolitis, and the other developed stenosis as a result of ischemic colitis induced by acute pancreatitis [195].

Pancreatitis in anorexia nervosa

Anorexia nervosa, a syndrome most commonly affecting young women, is characterized by weight less than 85 percent of weight that is considered normal for that person's age and height, distorted body image, and fear of becoming obese. It was presented a case of a 33-year-old woman with a 9-year history of anorexia nervosa. Her body mass index was 11.5 kg/m^2 of the time admission. Initial aminotransferase level was severely elevated, but it was normalized solely with improved nutrition and weight gain. Five and sixteen days after the admission urinary tract infection and elevation of pancreatic enzymes occurred. They were successfully treated with antibiotics and nutritional support. Fifty seven days after the admission, she discharged [196].

Subgroups of acute forms of pancreatitis

Gallstone-induced pancreatitis

Guidelines for treatment

All patients that presented with gallstone pancreatitis over a 4-year period to a Scottish hospital were audited retrospectively. Data were collated for radiological diagnosis within 48 hours, ERCP within 72 hours, CT at 6-10 days, and use of high-dependency or intensive therapy units in severe gallstone pancreatitis, and definitive treatment of gallstone pancreatitis within 2 weeks as recommended in national guidelines. Forty-six patients had severe gallstone pancreatitis and 54 patients mild pancreatitis. Etiology was established within 48 hours in 92 patients. Six (13 %) out of the patients with severe gallstone pancreatitis were managed in a high dependency unit. Fifteen (33 %) patients with severe gallstone pancreatitis underwent CT within 6-10 days of admission. Four (9 %) of the 46 patients with severe gallstone pancreatitis had urgent ERCP (less than 72 hours). Overall 22/100 patients unsuitable for surgery underwent endoscopic sphincterotomy as definitive treatment. Seventy-eight patients had surgery, with 40 (51 %) of these patients undergoing an index admission cholecystectomy, and 38 (49 %) patients were discharged for interval cholecystectomy. Overall 81 patients with gallstone pancreatitis had definitive therapy during the index to same admission (cholecystectomy or sphincterotomy). Two (5 %) patients were readmitted whilst awaiting interval cholecystectomy: one with acute cholecystitis and one with acute pancreatitis. There were no mortalities in this cohort. The study highlighted difficulties in implementation of national guidelines, as the use of critical care, timing of ERCP and CT, and definitive treatment prior to discharge did not concur with national targets for gallstone pancreatitis [197].

Impact on prognosis of ERCP ± EST

Danish guidelines recommend that patients with presumed severe gallstone-induced acute pancreatitis should receive endoscopic retrograde cholangiopancreatography (ERCP) within 72 hours. The results of a newly performed meta-analysis show that acute ERCP in patients with gallstone-induced acute pancreatitis does not reduce the risk of complications, and ERCP is therefore not to be used routinely in gallstone-induced acute pancreatitis patients. The possible benefits of replacing ERCP with either endoscopic ultrasonography or magnetic resonance cholangiopancreatograhy have yet to be demonstrated [198].

Early versus late cholecystectomy

In patients with biliary acute pancreatitis, cholecystectomy is mandatory to prevent further biliary events, but timing of cholecystectomy remains a subject of ongoing debate. The objective of the present, retrospective study was to compare the outcomes of early (within 2 weeks after onset of disease) versus delayed cholecystectomy in patients with biliary acute pancreatitis. Between 2000 and 2005, 112 patients underwent cholecystectomy because of biliary pancreatitis. Thirteen patients were excluded from analysis because of necrotizing pancreatitis on the initial computed tomography. Thirty-two were operated within 14 days (group A) and 67 after a longer time period (group B). The primary end point of the study was the rate of biliary complications before cholecystectomy. There were no differences regarding conversion rates to open surgery (6 % vs 3 %), local (3 % vs 4 %), or systemic complications (0 % vs 3 %), and mean postoperative stay (4.7 vs 5.7 days). Nevertheless, a greater rate of recurrent biliary pancreatitis was found in the group undergoing cholecystectomy later (0 % vs 13 %). It was concluded that the timing of cholecystectomy seems to have no clinically relevant effect on local or systemic complications, but delaying cholecystectomy is associated with an increase of biliary complications in patients with non-necrotizing biliary acute pancreatitis [199].

Precut at sphincterotomy

Precut is performed when biliary access at endoscopic retrograde cholangiopancreatography (ERCP) fails. Precut may have adjunctive risks, but some authors have suggested that the attempts to cannulate the papilla that precede precutting cause complications. It was therefore evaluated the role of the timing of precut in determining the development of complications and with respect to the other factors involved. During ERCP, after 10 min of attempts to cannulate, patients were randomized to an early-precut group (n=77) undergoing precut immediately or a late-access group (n=74) in which cannulation was attempted for 10 further minutes before the endoscopist was free to perform precut or to persist in cannulation. Occurrence of complications and the associated risk factors were recorded. The two groups were similar for general characteristics. The number of attempts to cannulate, the number of pancreas injections, and the incidence of acinarization were higher in the late-access group. The cannulation rate was 94 percent. The incidence of overall complications was similar, but the pancreatitis rate was higher in the late-access group (14.9 vs 2.6 %). Amylase levels increased by 399 $\pm$ 879 in the early-precut group and 834 $\pm$ 1478 in the late-access group, which was a significant difference. Nondilated bile duct and pancreatic injection were related to the development of pancreatitis, whereas the performance of precut was related to other complications. The authors concluded that early precut is associated with lower pancreatitis rate, suggesting that pancreatitis develops as a consequence of the attempts to cannulate the papilla and pancreatic injection, and not pre-cutting [200].

ERCP in severe biliary pancreatitis

Previous studies have included only a relatively small number of patients with predicted severe acute biliary pancreatitis in most studies. It was now again investigated the clinical effects of early ERCP in these patients in a prospective, observational multicenter study in 8 university medical centers and 7 major teaching hospitals. One hundred fifty-three patients with predicted severe acute biliary pancreatitis without cholangitis were enrolled in a randomized multicenter trial on probiotic prophylaxis in acute pancreatitis and were prospectively followed. Conservative treatment or ERCP within 72 hours after symptom onset (at discretion of the treating physician) were compared for complications and mortality. Patients without and with cholestasis (bilirubin: >2.3 mg/dL and/or dilated common bile duct) were analyzed separately. Of the 153 patients, 81 (53 %) underwent ERCP and 72 (47 %) conservative treatment. Groups were highly comparable at baseline. Seventy-eight patients (51 %) had cholestasis. In patients with cholestasis, ERCP (52/78 patients: 67 %), as compared with conservative treatment, was associated with significantly fewer complications (25 % vs 54 %). This included significantly fewer patients with >30 percent pancreatic necrosis (8 % vs 31 %). Mortality was nonsignificantly lower after ERCP (6 % vs 15 %). In patients without cholestasis, ERCP (29/75 patients: 39 %) was not associated with reduced complications (45 % vs 41 %) or mortality (14 % vs 17 %). It was concluded that early ERCP is associated with fewer complications in predicted severe acute biliary pancreatitis if cholestasis is present [201].

Value of EUS

When conventional ERCP methods fail because of periampullary or ductal obstruction, EUS-guided cholangiopancreatography (EUS-CP) may aid in pancreaticobiliary access. Consecutive patients undergoing EUS-CP were prospectively identified. These patients had undergone failed attempt(s) at therapeutic ERCP. Technical success was decompression of the duct of interest. Clinical success was resolution of jaundice or at least a 50 percent reduction in pain or narcotics, as applicable. Between 2003 and 2007, EUS-CP was attempted in 20 patients (11 men, 9 women age 58 years). Indications included jaundice (n=8), biliary stones (n=3), chronic pancreatitis (n=6), acute pancreatitis (n=2), and papillary stenosis (n=1). Reasons for failed ERCP included periampullary mass (n=8), intradiverticular papillae (n=4), and pancreatic duct stricture (n=7) or stone (n=1). Technical success was achieved in 18 of 20 patients (90 %). Biliary decompression was obtained in 11 of 12 patients (92 %) (7 transpapillary and 4 transenteric-transcholedochal). Pancreatic decompression

was obtained in 7 of 8 patients (88 %) (3 transpapillary, 4 transgastric). On follow-up, clinical improvement was noted in 15 of 20 patients (70 %). For treatment of pain associated with chronic pancreatitis, pain scores decreased. Complications (in 2 of 20) included perforation (n=1) and respiratory failure (n=1). It was concluded that a single-operator EUS-guided cholangiopancreatography provided decompression of obstructed ducts and may be performed after a failed attempt at conventional ERCP during the same endoscopic session [202].

Correlation between laboratory values and remaining common bile duct stone
An important question to be answered in all cases of acute biliary pancreatitis is whether or not a calculous biliary obstruction is still present. Answering this question conditions subsequent management, include the need for endoscopic retrograde cholangiopancreatography (ERCP). The aim of one study was to determine the relationship between persistent common bile duct stone (CBDS) and laboratory values, and dilation of bile duct in order to find possible significant associations in patients with acute biliary pancreatitis (ABP). It was retrospectively, statistical evaluated a group of 76 patients with ABP who had received early ERCP. The prevalence of choledocholithiasis in patients > 70 years old was 54 percent, in patients $\leq$ 70 years old it was 37 percent. Following cholecystectomy, CBDS was present in 82 percent of patients. The probability of CBDS occurrence in patients > 70 years old with bile duct dilation was 81 percent; in the absence of bile duct dilation CBDS was not present. The probability of CBDS occurrence in patients 70 years old with bile duct dilation was 58 percent, in the absence of bile duct dilation CBDS was present in 15 percent, which was a significant difference. In patients with bile duct dilation predictive factors were as follows: bilirubin, after excluding patients with acute cholecystitis and cholangitis; alanine aminotransferase in patients 70 years old; gamma-glutamyl transferase in patients > 70 years old. It was concluded that ERCP is indicated in patients with acute biliary pancreatitis if biliary obstruction is present and the presence of a ductal stone is suspected. From the results it is clear that the predictive parameter for choledocholithiasis is the dilation of the bile duct and previous cholecystectomy [203].

Mild biliary pancreatitis
Gallstones represent the most common cause of acute pancreatitis in Sweden. Epidemiological data concerning timing of cholecystectomy and sphincterotomy in patients with first attack of mild acute biliary pancreatitis (MABP) are scarce. Our aim was to analyse readmissions for biliary disease, cholecystectomy within one year, and mortality within 90 days of index admission for MABP. Hospital discharge and death certificate data were linked for patients with first attack acute pancreatitis in Sweden 1988-2003. Mortality was calculated as case fatality rate (CFR) and standardized mortality ratio (SMR). MABP was defined as acute pancreatitis of biliary aetiology without mortality during an index stay of 10 days or shorter. Patients were analysed according to four different treatment policies: Cholecystectomy during index stay (group 1), no cholecystectomy during index stay but within 30 days of index admission (group 2), sphincterotomy but not cholecystectomy within 30 days of index admission (group 3), and neither cholecystectomy nor sphincterotomy within 30 days of index admission (group 4). Of 11636 patients with acute biliary pancreatitis, 8631 patients (74 %) met the criteria for MABP. After exclusion of those with cholecystectomy or sphincterotomy during the year before index admission (n=212), 8419 patients with MABP remained for analysis. Patients in group 1 and 2 were significantly younger than patients in group 3 and 4. Length of index stay differed significantly between the groups, from 4 (3-6) days, (representing median, 25 and 75 percentiles) in group 2 to 7 (5-8) days in groups 1. In group 1, 4.9 percent of patients were readmitted at least once for biliary disease within one year after index admission, compared to 100 percent in group 2, 63 percent in group 3, and 76mpercent in group 4. One year after index admission, 31 percent of patients in group 3 and 48 percent of patients in group 4 had undergone cholecystectomy. SMR did not differ between the four groups. It was concluded that cholecystectomy during index stay slightly prolongs this stay, but drastically reduces readmissions for biliary

indications [204].

Hypercalcemia-induced pancreatitis

Hypercalcemia due to hyperparathyroidism is a rare etiology for acute pancreatitis, oscillating between 1.5 and 7 percent in the different series. Although the cause-effect relationship and the pathophysiology of the condition are not clear, it seems that the association among them is not incidental, and serum calcium could be a major risk factor, so that pancreatitis would come to occur during severe hypercalcemia attacks. Mutations in different genes have been proposed as well to justify why only some patients with primary hyperparathyroidism and hypercalcemia develop acute pancreatitis. References to cases like these ones are rare in the literature. It was reported two patients with acute pancreatitis associated with hyperparathyroidism and hypercalcemia, one of them with a fatal outcome [205].

Hypercalcemia is an important etiology to consider in the evaluation of acute pancreatitis. Not only is it a treatable cause, but understanding the basis for this etiology may provide new insight into the common biochemical mechanisms involved in the pathogenesis of pancreatitis. It was reported a case of an 11-year-old girl with hypercalcemia due to primary hyperparathyroidism who developed recurrent pancreatitis [206].

Alcohol-induced pancreatitis

The aim of one study was to investigate the association between lifetime consumption of alcoholic beverages and cancer risk. Data were collected in a population-based case-control study, conducted in Montreal in the mid-1980s, designed to assess the associations between hundreds of non-occupational and occupational exposures and multiple cancer sites in men. It was presented results for 13 cancer sites 83 patients with pancreas cancer in comparison to population controls (n=507). Odds ratios (OR) were estimated for the associations between lifetime consumption of total alcoholic beverages, beer, wine, and/or spirits, altogether and separately, and each cancer site, while carefully adjusting for smoking and other covariates using polytomous logistic regression. For several cancers (oesophagus, stomach, colon, liver, pancreas, lung, prostate) there was evidence of increased risk among alcohol consumers compared with abstainers and occasional drinkers. For most sites, it was beer and to a lesser extent spirits consumption that drove the excess risks. The results support the hypothesis that moderate and high alcohol intake levels over the lifetime might increase cancer risk at several sites [207].

During 2006 to 2007, 78 patients with acute pancreatitis were prospectively searched for the etiology by:

- Performing liver chemistry tests and transabdominal ultrasonography (US) for gallstone in every case
- Measuring serum triglyceride and calcium in every case
- Investigating definite drugs use or other identified etiology
- Asking about the amount of alcohol ingestion (amount > 80 g/day for > 5 years was required for alcoholic AP
- Performing CT scan (if age > 40 years) and EUS if no etiology was identified.

Of the 78 patients, the etiologies were alcohol in 32 (41 %), gallstones in 29 (37 %), miscellaneous in 13 (1 7%) and idiopathic acute pancreatitis in 4 patients (5 %). Among the 45 patients of the study period (58 %) who consumed alcohol more than the defined threshold for alcoholic acute pancreatitis, 13 (29 %) were found to have other explainable causes of pancreatitis, i.e gallstones in 10, hypertriglyceridemia in 2 and AIDS cholangiopathy in 1 patient. The authors concluded that alcohol was probably over-

diagnosed as a leading etiology of pancreatitis in the past. One-fourth of AP patients who were heavy drinkers had other explainable etiologies of acute pancreatitis [208].

In the long term, half of patients with their first alcohol-associated acute pancreatitis develop acute recurrence, alcohol consumption being the main risk factor. None of the recent national or international guidelines for treatment include recommendations aimed to decrease recurrences, possibly because of a lack of studies. One study investigated whether acute recurrences can be reduced. One hundred and twenty patients admitted to a university hospital for their first alcohol-associated acute pancreatitis were randomized either to repeated intervention (n=59) or initial intervention only (n=61). The patients in the two groups did not differ. A registered nurse performed an intervention in both groups before discharge, after which it was repeated in the study group at 6-month intervals at the gastrointestinal outpatient clinic. Acute recurrences during the next 2 years were monitored. There were 9 recurrent pancreatitis episodes in 5 patients in the repeated-intervention group compared with 20 episodes in 13 patients in the control group, which was a signifikant difference. The recurrence rates were similar during the first 6 months (4 vs 5 episodes), after which the repeated-intervention group had significantly fewer recurrences than the control group (5 vs 15 episodes). It was concluded that the repeated visits at 6-month intervals at the gastrointestinal outpatient clinic, consisting of an intervention against alcohol consumption, appear to be better than the single standardized intervention alone during hospitalization in reducing the development of recurrent acute pancreatitis during a 2-year period [209].

Acute alcoholic pancreatitis (AAP) recurs in up to half of the patients, continuous alcohol consumption being an important risk factor. Changes in pancreatic function and morphology after acute pancreatitis have been characterized previously, but their association with later recurrences has not been adequately studied. In a prospective follow-up study, the pancreatic function of 54 patients (47 males and 7 females) with a median age of 49 years (range 25-71) and morphology (35 patients) were evaluated. Pancreatic morphology was evaluated by secretin-stimulated magnetic resonance pancreatography (SMRP). Patients were evaluated early (baseline) and at 2 years after the first episode of AAP. In order to evaluate later recurrences, the patients were followed for a median of 47 (range 28-66) months. Of the 46 patients without previous diabetes, 17 patients (37 %) developed impaired glucose metabolism during the 2 years following the first AAP. The prevalence of exocrine dysfunction decreased from 39 percent at baseline to 9 percent at 2 years. Of the patients with severe pancreatitis (n=13, 24 %), 31 percent had elevated glycosylated haemoglobin levels compared to 7 percent in patients with mild pancreatitis (odds ratio 5.5, 95 % confidence interval 1.04 to 29.0]. Twenty percent (7/35) of the patients had changes consistent with chronic pancreatitis on baseline SMRP, which persisted in all cases. Of the 29 percent of patients with acute changes on baseline SMRP, the acute changes resolved in 50 percent and chronic pancreatitis was detected in the remaining 50 percent at 2 years. Development of chronic changes did not depend on continued alcohol consumption, as it was also found in three patients practising complete abstinence following their first attack of AAP. The presence of a chronic pseudocyst at 2 years predicted pancreatitis when compared to patients lacking pseudocyst formation: 4 (80 %) versus 5 (17 %) (odds ratio 20 95 % confidence interval 1.83 to 219). It was concluded taht the severity of the first episode of AAP was associated with deteriorated diabetes control, but not with pancreatic exocrine dysfunction at 2 years. The number of patients with chronic changes on SMRP increased independently of alcohol consumption. Chronic pseudocyst formation seen on SMRP 2 years after AAP was significantly associated with recurrence of pancreatitis [210].

Post-ERCP-pancreatitis

Prophylactic effect of allupurinol

To assess the efficacy of allopurinol to prevent hyperamylasemia and pancreatitis after

endoscopic retrograde cholangiopancreatography 170 patients were enrolled and randomized to two groups: a study group (n=85) who received 300 mg of oral allopurinol at 15 h and 3 h before endoscopic retrograde cholangiopancreatography (ERCP) and a control group (n=85) receiving an oral placebo at the same times. Main Outcome Measurements included serum amylase levels and the number severity of the episodes of pancreatitis. Serum amylase levels were classified as normal (< 150 IU/L) or hyperamylasemia (> 151 IU/L). Episodes of pancreatitis were classified following Ranson's criteria and CT severity index. Distribution of benign pathology was similar between groups. Hyperamylasemia was more common in the control group. Mild pancreatitis developed in two patients from the study group (2.3 %) and eight (9.4 %) from control group, which was a significant difference; seven episodes were observed in high-risk patients of the control group (25 %) and one in the allopurinol group (3 %). Significant risk factors for post-procedure pancreatitis were precut sphincterotomy, pancreatic duct manipulation, and multiple procedures. There were no deaths or side effects. It was concluded that allopurinol before ERCP decreased the incidences of hyperamylasemia and pancreatitis in patients submitted to high-risk procedures [211].

Sprayed epinephrine as prophylaxis

Epinephrine sprayed on the papilla may reduce papillary edema and thus prevent acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). The aim of one study was to determine the efficacy of this technique for prevention of post- ERCP pancreatitis. It was randomized the patients to have 10 ml of either 0.02 percent epinephrine (epinephrine group) or saline (control group) sprayed on the papilla after diagnostic ERCP and prospectively analyzed the occurrence of post-ERCP pancreatitis between the groups. There was no significant difference between the groups with regard to visualization of the bile duct and/or the main and accessory pancreatic ducts, presence of pancreatic acinarization, number of injections into the pancreatic duct, total volume of contrast used, and procedure duration. Overall, post-ERCP pancreatitis occurred in 4 of the 370 patients (1 %). The incidence of pancreatitis tended to be higher in the control group (4/185) than in the epinephrine group (0/185), but this was not a statistically significant difference. Further studies on the efficacy of this technique in patients at high risk for pancreatitis, and on other volumes and/or concentrations of epinephrine, are warranted [212].

Interleukin-10 as prophylaxis

Pancreatitis is the most common major complication of endoscopic retrograde cholangiopancreatography (ERCP). Inflammatory cytokines are released during acute pancreatitis. Interleukin-10 (IL-10) is a potent inhibitor of cytokines and has been shown to attenuate pancreatitis in animal models and pilot human studies. One study aimed to determine whether prophylactic IL-10 administration reduces the frequency or severity of post-ERCP pancreatitis in high-risk patients. A randomized, multicenter, double-blind, placebo-controlled study was conducted. Patients received IL-10 at a dose of either 8 or 20 microg/kg or placebo as a single intravenous injection 15 to 30 minutes before ERCP. Standardized criteria were used to diagnose and grade the severity of postprocedure pancreatitis. A total of 305 of the planned total enrollment of 948 patients were randomized. There was a 15, 22, and 14 percent incidence of post-ERCP pancreatitis in the IL-10 (8 microg/kg), IL-10 (20 microg/kg), and placebo treatment groups, respectively. Due to apparent lack of efficacy, the study was terminated at an interim analysis [213].

Antibiotics as prophylaxis

It was determined the prophylactic effect of antibiotics on post-endoscopic retrograde cholangiopancreatography (ERCP) cholangitis or sepsis reduction in randomized controlled trials. Databases including MEDLINE, EMBASE, Cochrane Library, and Science Citation Index updated to June 2007 were searched. Main outcome measure was post-ERCP cholangitis or sepsis. Seven trials were identified, and a total of 1389 patients were included; post-ERCP cholangitis occurred in 5.8 percent of controls (41/705) versus 3.4 percent of

treated patients (23/684), without statistical significance (relative risk [RR], 0.58; 95 % confidence interval [CI], 0.22 tgo 1.55). Subsequent sensitivity analysis on trials mainly targeted at patients with suspicious biliary obstruction showed that the incidences of post-ERCP cholangitis were 2.8 percent (12/425) and 5.4 percent (24/441) in the antibiotics and control groups, respectively, and this sensitivity analysis did not support antibiotics' preventive effect (RR, 0.33; 95 % CI, 0.03 to 3.32). Another sensitivity analysis exclusively including trials with intravenous route of antibiotics administration also failed to confirm the prophylactic effect of antibiotics (RR, 0.53; 95 % CI, 0.18 to 1.60). It was concluded that antibiotics cannot significantly prevent ERCP-induced cholangitis in unselected patients and should not be routinely recommended [214].

To determine the prophylactic effect of antibiotics on post-endoscopic retrograde cholangiopancreatography (ERCP) cholangitis or sepsis reduction in randomized controlled trials a search was done in databases including MEDLINE, EMBASE, Cochrane Library, and Science Citation Index updated to June 2007. Main outcome measure was post-ERCP cholangitis or sepsis. Seven trials were identified, and a total of 1389 patients were included; post-ERCP cholangitis occurred in 5.8 percent of controls (41/705) versus 3.4 percent of treated patients (23/684), without statistical significance. Subsequent sensitivity analysis on trials mainly targeted at patients with suspicious biliary obstruction showed that the incidences of post-ERCP cholangitis were 2.8 percent (12/425) and 5.4 percent (24/441) in the antibiotics and control groups, respectively, and this sensitivity analysis did not support antibiotics' preventive effect. Another sensitivity analysis exclusively including trials with intravenous route of antibiotics administration also failed to confirm the prophylactic effect of antibiotics [215].

TAP for monitoring post-ERCP-pancreatitis

Trypsinogen activation peptide (TAP) is a small peptide of 7 to 10 amino acids capable of activating trypsinogen into trypsin, and it reflects the amount of activated trypsinogen. Serum TAP concentrations determined before and 6 hours after ERCP did not differ probably because the half-life of TAP is approximately 8 minutes, and this time interval is too long to detect its alteration. Therefore, the primary end point of the study was to evaluate the hourly TAP concentration elevation after ERCP. All consecutive patients who underwent interventional ERCP from 2005 to 2007 were studied. Post-ERCP acute pancreatitis was defined as the appearance of typical abdominal pain associated with an increase in serum amylase activity greater than 3 times the upper reference limit. Elevation of serum TAP concentration was estimated in 30 percent of patients who developed postprocedural acute pancreatitis. It was enrolled 75 patients (38 men and 37 women). The reasons for which they underwent operative ERCP were cholangitis or jaundice in 63 patients (84 %), the need to insert a biliary stent in 4 (5 %), persistent pain or jaundice in 6 patients (8 %) with recurrent pancreatitis, and the need to insert a pancreatic stent in 2 (3 %). The mean endoscopic procedure lasted for 45 minutes (range, 15-95 minutes). There was difficult cannulation in 29 patients (39 %); Wirsung injection in 40 (53 %); mechanic lithotripsy in 2 (3 %); biliary sphincterotomy in 44 (59 %); major papilla pancreatic sphincterotomy in 6 (8 %); minor papilla sphincterotomy in 2 (3 %); and insertion of endoscopic biliary drainage in 23 (31 %), of pancreatic drainage in 6 (8 %), of a biliary stent in 17 (23 %), and of a pancreatic stent in 3 (4 %). Sixty-one patients (81 %) received intravenous gabexate mersilat as a prophylactic treatment to prevent postprocedural ERCP. Postprocedural abdominal pain was recorded at 1 hour in 35 patients (47 %), 2 hours in 34 (45 %), 3 hours in 14 (19 %), 4 hours in 8 (11 %), and 6 hours in another 8 (11 %); 6 patients (8 %) had pain for more than 6 hours. Postprocedural acute pancreatitis developed in 13 patients (17 %), and it was in all of them clinically mild. The frequency of patients with acute pancreatitis who had pain after 2 hours (11/13; 85 %) was significantly higher when compared with patients without acute pancreatitis (23/62; 37 %). Postprocedural acute pancreatitis developed in 20 % (12/61) of patients who received gabexate and 7 percent (1/14) of those who did not, which was a not significant difference. In the 65 patients who completed the study, at basal examination

(before ERCP), serum TAP was detectable in all patients. One- and 2-hour post-ERCP serum TAP concentrations remained elevated, whereas these concentrations significantly declined at 4 hours. Urine TAP showed the same behavior as serum TAP; detectable urine concentrations were present in 6 (9 %) of the 65 patients before ERCP and after 2 hours, whereas at 4 and 6 hours, all patients had no detectable urinary TAP concentrations. 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 behaviour was present between patients who were treated prophylactically with gabexate and those who did not receive the drug. Regarding the primary end point, all patients had detectable concentrations of serum and urine TAP before ERCP, and no differences in basal TAP values were observed among patients with lithiasis of the common bile duct, those with benign stenosis of the common bile duct, those with chronic pancreatitis, and those with common bile duct pancreatic neoplasms. The serum concentrations of TAP remained elevated for the subsequent observation period (at 1 and 2 hours) and then progressively declined at 3, 4, and 6 hours. This observation confirms data on the low sensitivity of serum TAP in diagnosing acute pancreatitis because TAP is rapidly eliminated from the circulation. Urine TAP gave the same results [216].

Ischemic pancreatitis

Acute pancreatitis due to pancreatic ischemia is a rare condition. In a case report it was described a 57-year-old male who developed an acute necrotizing pancreatitis after running a marathon and visiting a sauna the same evening, with an inadequate fluid and food consumption during both events. Pancreatic ischemia imposed by mechanical and physical stress and dehydration can induce the development of acute pancreatitis. Separately, these factors are rare causes of ischemic acute pancreatitis. But when combined, as in this particular case, the risk of an acute necrotizing pancreatitis cannot be neglected [217].

Drug-induced pancreatitis

It was reported a case of a 35-year-old patient with acute pancreatitis after administration of ceftriaxone. She was given ceftriaxone (2g/day) for 9 days because of diverticulitis of the colon but was admitted to our hospital again because of epigastralgia 12 days after the first administration of ceftriaxone. Laboratory examination showed markedly elevated serum amylase, and CT scan demonstrated findings consistent with acute pancreatitis, in addition to sludge in the common bile duct and gall bladder, which was not identified before the administration of ceftriaxone. One may be aware of the fact that administration of ceftriaxone sometimes results in the formation of biliary sludge and can cause severe adverse events such as cholecystitis and pancreatitis, not only in children, but also in adult patients [218].

Infective pancreatitis

Ascaris

Ascaris lumbricoides infestations are endemic in tropical countries. Ascaris lumbricoides can occasionally cause biliary obstruction and result in obstructive jaundice or pancreatitis. It was present a 34-year-old Bangladeshi woman with biliary ascariasis, resulting in recurrent pancreatitis. Her diagnosis was made with endoscopic retrograde cholangiopancreatography performed during an acute attack of pain [219].

Brucellosis

Brucellosis is an acute, subacute or chronical disease, from the zoonosis group, caused by various types of bacteria belonging to genus Brucellae. It is transmitted to humans from domestic animals: goats, sheep, cattle, pigs and dogs. The course of the disease may either be asymptomatic, or produce a variety of clinical manifestations, ranging from light ones to extremely severe clinical forms. The aim of one study was to follow the clinical features of brucella infection in the hospital-treated patients, as well as its course and outcome. The investigation included 15 patients, treated for brucella infection during the last two years (2004 and 2005). All patients were adults, their age ranged from 18 to 71, 50 on average. The epidemiological questionnaire was positive in all patients, confirming contacts with the ailing animals, or consumption of cheese made from milk of diseased animals. They all exhibited the classic symptoms: increased body temperature and shiver, fever, sweating, malaise and headache, the so called flu like state. The serum agglutination test was positive in respect to brucellosis, the titre ranged from 1:80 to 1:1280. Eight patients suffered excessive back pain, accompanied with impeded walk. In half of them magnetic resonance imaging confirmed the spondylodiscitis diagnosis. Three patients had clinical features of knee arthritis, two had bronchopneumonia, one pancreatitis, and one developed the signs of an acute kidney insufficiency. The outcome was favourable in all patients. They recuperated or healed completely. In one patient a relapse occurred, leading to the chronic course of the illness. Although predominantly Mediterranean Brucellosis is a worldwide spread disease [220].

Leptospirosis

Even though leptospiral infection is not uncommon, it can have different rare presentations. Acute pancreatitis is one such rare gastrointestinal manifestation of acute pancreatitis. Apart from the typical clinical features; elevated serum lipase or elastase-1, along with radiological evidence and positive leptospiral serology confirms this rare association [221].

Attempts to non-surgical treatment

Enteral nutrition

Although the benefits of enteral nutrition in acute pancreatitis are well established, the optimal composition of enteral feeding is largely unknown. The aim of one study was to compare the tolerance and safety of enteral nutrition formulations in patients with acute pancreatitis. Electronic databases (Scopus, MEDLINE, Cochrane Controlled Clinical Trials Register) and the proceedings of major pancreatology conferences were searched. Twenty randomized controlled trials, including 1070 patients, met the inclusion criteria. None of the following was associated with a significant difference in feeding intolerance: the use of (semi)elemental versus polymeric formulation (relative risk 0.62; 95 percent confidence interval 0.10 to 3.97); supplementation of enteral nutrition with probiotics (relative risk 0.69; 95 percent confidence interval 0.43 to 1.09); or immunonutrition (relative risk 1.60; 95 percent confidence interval 0.31 to 8.29). The risk of infectious complications and death did not differ significantly in any of the comparisons. It was concluded that the use of polymeric, compared with (semi)elemental, formulation does not lead to a significantly higher risk of feeding intolerance, infectious complications or death in patients with acute pancreatitis. Neither the supplementation of enteral nutrition with probiotics nor the use of immunonutrition significantly improves the clinical outcomes [222].

Plasmapheresis of triglycerides

It was presented case report shows hypertriglycerydemia treatment problem in 26-year-old woman with 2 episodes of acute pancreatitis history. Very high serum triglycerides

concentration and clinical symptoms suggested chylomicronemia syndrome with urgent need for treatment. After a course of several subsequent therapeutic plasmapheresis triglycerides significantly decreased. Safety and effectiveness of this method was confirmed [223].

Intravenous protease inhibitors

Severe acute pancreatitis is poor prognosis. Continuous regional arterial infusion of protease inhibitors and antibiotics were developed in Japan. It was evaluated whether arterial infusion both celiac artery and superior mesenteric artery for this disease would reduce mortality. Seventeen patients were treated arterial infusion of protease inhibitor and antibiotics via both celiac artery and superior mesenteric artery. Changes of Acute Physiology and Chronic Health Evaluation II score and mortality were evaluated. Arterial infusion via two routes reduced the mortality rate and improved Acute Physiology and Chronic Health Evaluation II score. The overall mortality rate was 12 percent. The mortality rate in patients in those that were treated within 3 days after the onset was significantly lower than that in patients in whom were treated without 3 days after the onset. Arterial infusion via superior mesenteric artery might prevent both bacterial translocation and non-occlusive mesenteric ischemia. Continuous arterial infusion both celiac artery and superior mesenteric artery might be effective for reducing mortality and preventing the development of pancreatitis, especially when initiated within 3 days after the onset [224].

Dialysis as a treatment for acute pancreatitis

The aim of one study was to study the therapeutic effects and the mechanism of combination of hemofiltration (HF) and peritoneal dialysis (PD) in the treatment of severe acute pancreatitis (SAP). Fifty-one cases of severe acute pancreatitis were randomly divided into the HF+PD group (treated group, 36 patients) and the non-HF+PD group (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 HF+PD treatment, were decreased significantly compared with those observed in pretherapy and the control group. It was concluded that inflammatory cytokines, which overproduced in SAP, can be eliminated effectively from the blood and the ascites by HF+PD treatment [225].

Peritoneal lavage

The evaluation of precocious and prolonged lavage and drainage by laparoscopic approach in the treatment of severe acute pancreatitis was studied 2006-2008 on a sample consisting of 35 subjects with the severe acute pancreatitis that was divided into two lots. One lot was formed by 16 patients whom were applied the method mentioned ahead and in the B lot, 19 patients, treated by conventional and known methods of treatment. The method proposed, completed about laparoscopic approach in a third day of admission, consists, after setting lesional balance, in lavage of peritoneal space and mounting two tubes drainage, one subhepatic space and the other in Douglas space. Peritoneal lavage discontinuous with physiological serum was done during 7 days. For an accurate assessment may were determined serum and peritoneal concentrations of interleukin 6. The duration of organic dysfunction was 8 days for A lot subjects and 18 days for B lot subjects. The mortality at A lot

was 13 percent (n=2) and at lot B 37 percent (n=7). The tardive mortality by sepsis was null at subjects with lavage and was 16 percent (n=3) at subjects without lavage. The precocious mortality was 13 percent (n=2) in the A lot and 21 percent (n=4) in the lot B. The average hospitalization was 26 days in subjects with peritoneal lavage and 36 days in those treated conservatively, the difference is statistically significant. The method has proved not generating of morbidity and supplementary mortality. Study of the variation of serum and peritoneal concentrations of interleukin 6 shows the modulator effect of the peritoneal lavage early and prolonged of the inflammatory response and offers an argument of the inefficiency of short peritoneal lavage [226].

Probiotics

A cohort study of 731 patients with a primary episode of acute pancreatitis in 2004-2007, including 296 patients involved in a randomized controlled trial to investigate the value of probiotic treatment in severe pancreatitis, was evaluated regarding time of onset of bacteraemia, pneumonia, infected pancreatic necrosis, persistent organ failure and death were recorded. The initial infection in 173 patients was diagnosed a median of 8 (interquartile range 3-20) days after admission (infected necrosis, median day 26; bacteraemia/pneumonia, median day 7). Eighty percent of 61 patients who died had an infection. In 154 patients with pancreatic parenchymal necrosis, bacteraemia was significantly associated with increased risk of infected necrosis (65 vs 38 %). In 98 patients with infected necrosis, bacteraemia was associated with higher mortality (40 vs 16 %). In multivariable analysis, persistent organ failure (odds ratio 18.0), bacteraemia (odds ratio 3.4) and age (odds ratio 1.1) were associated with death. It was concluded that infections occur early in acute pancreatitis, and have a significant impact on mortality, especially bacteraemia [227].

To determine the relation between intestinal barrier dysfunction, bacterial translocation, and clinical outcome in patients with predicted severe acute pancreatitis and the influence of probiotics on these processes a randomized, placebo-controlled, multicenter trial on probiotic prophylaxis (Ecologic 641) in patients with predicted severe acute pancreatitis was performed (PROPATRIA). Excretion of intestinal fatty acid binding protein (IFABP, a parameter for enterocyte damage), recovery of polyethylene glycols (PEGs, a parameter for intestinal permeability), and excretion of nitric oxide (NOx, a parameter for bacterial translocation) were assessed in urine of 141 patients collected 24 to 48 h after start of probiotic or placebo treatment and 7 days thereafter. IFABP concentrations in the first 72 hours were significantly higher in patients who developed bacteremia, infected necrosis, and organ failure. PEG recovery was significantly higher in patients who developed bacteremia (PEG 4000), organ failure (PEG 4000), or died (PEG 4000). Probiotic prophylaxis was significantly associated with an increase in IFABP (median 362 vs 199 pg/mL), most evidently in patients with organ failure, and did not influence intestinal permeability. Overall, probiotics decreased NOx but, in patients with organ failure, increased NOx. It was concluded that bacteremia, infected necrosis, organ failure, and mortality were all associated with intestinal barrier dysfunction early in the course of acute pancreatitis. Overall, prophylaxis with this specific combination of probiotic strains reduced bacterial translocation, but was associated with increased bacterial translocation and enterocyte damage in patients with organ failure [228].

It has been proposed that probiotics can favorably influence the course of critically ill patients with acute pancreatitis. To address this question, a limited systematic review was undertaken (MEDLINE search for articles published in English) to identify randomized, controlled trials that compared a group of critically ill patients taking probiotics with a group that did not. Ten such trials, mostly with high risks of methodologic bias, were identified. When the data were combined, the probiotics did not appear to influence mortality or duration of hospitalization.

However, the recipients of the probiotics had fewer infectious episodes (absolute risk differente -21 %). This effect was seen particularly in trials employing one combination of probiotic agents (Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei, Lactobacillus plantarum). Unfortunately, this effect may be overly optimistic, as methodologic shortcomings could have introduced biases into the trials. Three trials of patients with severe acute pancreatitis were not included in this primary analysis because not all of the patients were in the intensive care unit. The largest of these, and the one with the lowest risk of bias, demonstrated that probiotics increased mortality, in part because of the precipitation of ischemic bowel disease (in patients who were also receiving postpyloric enteral nutrition infusions). Probiotics also appeared to reduce the incidence of antibiotic-associated diarrhea in hospitalized patients, although these trials did not specifically focus only on those who were critically ill. In summary, it is not clear that probiotics are beneficial (and they may even be harmful) in the critically ill patient group [229].

Antibiotics

The aim of one study was to analyze the evidence-based use of antibiotic therapy in the treatment of acute pancreatitis and to identify factors influencing the introduction of antibiotic therapy in the setting of transitional country clinical hospital. A retrospective study was conducted from hospital records of patients treated for acute pancreatitis during 2005. Data collected from patients' histories were compared with indications for antibiotic treatment and antibiotics with demonstrated therapeutic efficacy in acute pancreatitis which were obtained from published literature. Antibiotic therapy was used in 68 percent of patients with acute pancreatitis. Combination of amoxicillin plus clavulanic acid was most frequently administered, either as monotherapy or in combination with metronidazole and/or gentamicin (37 %), followed by cefuroxime (33 %) and cefoperazone (27 %). The choice of antibiotic was appropriate in 36 perent of study patients; however in 30 percent of patients who were administered antibiotics had no indication for this therapy; and 47 percent of patients who had indications for receiving antibiotic therapy didn't receive it. In the groups of patients treated with antibiotics, the cost of treatment was significantly higher compared to groups of patients who were not treated with antibiotics. In addition to antibiotic therapy, the cost of treatment was significantly influenced by the length of hospital stay and treatment at intensive care unit. The use of antibiotics in the setting of transitional country university hospital in patients with acute pancreatitis is not evidence-based. Decision on the introduction of antibiotic therapy is not based on objective parameters of disease severity or evidence of therapeutic efficacy of particular antibiotics. The cost of treatment is significantly increased by the use of antibiotic therapy [230].

Necrosectomy

Traditional open surgical necrosectomy for treatment of infected pancreatic necrosis is associated with high morbidity and mortality, leading to a shift toward minimally invasive endoscopic, radiologic, and laparoscopic approaches. Percutaneous drainage is useful as a temporizing method to control sepsis and as an adjunctive treatment to surgical intervention. It is limited because of the requirement for frequent catheter care and the need for repeated procedures. Endoscopic transgastric or transduodenal therapies with endoscopic debridement/necrosectomy have recently been described and are highly successful in carefully selected patients. It avoids the need for open necrosectomy and can be used in poor operative candidates. Laparoscopic necrosectomy is also promising for treatment of pancreatic necrosis. However, the need for inducing a pneumoperitoneum and the potential risk of infection limit its usefulness in patients with critical illness. Retroperitoneal access with a nephroscope is used to directly approach the necrosis with complete removal of a sequestrum. Retroperitoneal drainage using the delay-until-liquefaction strategy also appears

to be successful to treat pancreatic necrosis. The anatomic location of the necrosis, clinical comorbidities, and operator experience determine the best approach for a particular patient. Tertiary care centers with sufficient expertise are increasingly using minimally invasive procedures to manage pancreatic necrosis [231].

Minimal invasive methods

Infection of pancreatic necrosis is a life-threatening complication during the course of acute pancreatitis. In critically ill patients, surgical or extended endoscopic interventions are associated with high morbidity and mortality. Minimally invasive procedures on the other hand are often insufficient in patients suffering from large necrotic areas containing solid or purulent material. It was presented a strategy combining percutaneous and transgastric drainage with continuous high-volume lavage for treatment of extended necroses and liquid collections in a series of patients with severe acute pancreatitis. Seven consecutive patients with severe acute pancreatitis and large confluent infected pancreatic necrosis were enrolled. In all cases, the first therapeutic procedure was placement of a CT-guided drainage catheter into the fluid collection surrounding peripancreatic necrosis. Thereafter, a second endosonographically guided drainage was inserted via the gastric or the duodenal wall. After communication between the separate drains had been proven, an external to internal directed high-volume lavage with a daily volume of 500 ml up to 2,000 ml was started. In all patients, pancreatic necrosis/liquid collections could be resolved completely by the presented regime. No patient died in the course of the study. After initiation of the directed high-volume lavage, there was a significant clinical improvement in all patients. Double drainage was performed for a median of 101 days, high-volume lavage for a median of 41 days. Several endoscopic interventions for stent replacement were required (median 8). Complications such as bleeding or perforation could be managed endoscopically, and no subsequent surgical therapy was necessary. All patients could be dismissed from the hospital after a median duration of 78 days. This approach of combined percutaneous or endoscopic drainage with high-volume lavage shows promising results in critically ill patients with extended infected pancreatic necrosis and high risk of surgical intervention. Neither surgical nor endoscopic necrosectomy was necessary in any of our patients [232].

Minimally invasive necrosectomy is an umbrella term encapsulating the retroperitoneal, endoscopic and laparoscopic approaches which all share the common goal of avoidance of the physiological insult of the traditional “open” laparotomy approach to necrosectomy. However, there is no randomised trial evidence comparing these techniques meaning that current evidence is unclear in terms of which approach to select in any particular setting. Patients with pancreatic necrosis represent individuals at high risk for adverse outcome and should be managed by a multidisciplinary team in a specialist unit. At a minimum, there should be input from surgical, radiological, and gastroenterological experts. Procedures must not be selected simply on the expertise of a single discipline. Specialist care should reflect evidence from the open necrosectomy era that is likely to translate to minimally invasive interventions. In contemporary pancreatic surgical practice, magnetic resonance (MR) scanning provides additional diagnostic information (in addition to computed tomography and endoscopic ultrasonography) in the critical later stages of pancreatic sepsis and in particular in relation to the fluid/solid components of necrosis. Although it could be argued that MR is not widely available and that CT remains the gold-standard test, an equally valid counterargument is that complex, novel approaches to pancreatic necrosis should not be adopted in units that are not comprehensively equipped. With staging information to hand, a broad categorization can be made into individuals with predominantly solid necrosis and those with fluid-predominant collection. In the former category, collections tracking to the left paracolic gutter and retroperitoneum are in the category wherein good outcomes have been reported from image-guided placement of guidewires, the Seldinger technique for placement of drains followed by retroperitoneal necrosectomy. The retroperitoneal approach seems far

less safe for predominantly cephalic collections because of the proximity of the portal/superior mesenteric venous confluence. In the setting of retrogastric collections which are “fluid predominant” (including the type of collection recently termed “walled off pancreatic necrosis”) there is equipoise between laparoscopic and endoscopic approaches. Current evidence in relation to timing of surgery, use of fine-needle aspiration and detailed imaging by magnetic resonance scanning is incorporated into a modern treatment algorithm. With these constraints in place, there may be some advantages inherent to each approach: the endoscopic approach with a side-viewing duodenoscope allows opportunities for radiological delineation of the relationship between the fluid collection and the main pancreatic duct and also for assessment of the integrity of the main duct; laparoscopic debridement allows the lesser sac to be examined under direct vision and the use of high-flow irrigation with piecemeal necrosectomy. Combinations of these approaches – “laparo-endoscopic” approaches – have also been reported. Radiologically guided percutaneous drainage is also a recognised option: simple or passive external drainage can be used in the setting of salvage for a critically ill patient whilst more active percutaneous drainage with tract dilatation and irrigation can be used as a means of achieving necrosectomy. Open necrosectomy still retains a place in this hierarchy of care: patients with a clinical suspicious of ischaemic intestine or colonic complications of pancreatitis are invariably treated by urgent open laparotomy. Further, patients with multi-loculated intra-peritoneal collections together with lesser sac or retroperitoneal sepsis may be best addressed by open surgery. It is thus concluded that the era of minimally invasive necrosectomy has arrived. In the absence of randomised trial evidence, the keys to contemporary management of pancreatic necrosis are good multidisciplinary care, adequate high-quality imaging and careful consideration of all available treatment options including traditional open approaches [233].

While sterile pancreatic necrosis should be managed conservatively, infected pancreatic necrosis requires debridement and drainage supplemented by antibiotic therapy. Surgical necrosectomy is the traditional approach, but less invasive techniques (retroperitoneal or laparoscopic necrosectomy, computed tomography-guided percutaneous catheter drainage) may be equally effective [234].

Intraparenchymal pancreatic air

Emphysematous pancreatitis is characterized by the presence of intraparenchymal pancreatic air in the setting of necrotizing pancreatitis. Mortality and morbidity rates approach approximately 40 percent and 100 percent, respectively. Traditionally, emphysematous pancreatitis was an indication for surgical intervention. The purpose of one review was to discuss the experience with nonoperative management of emphysematous pancreatitis. Between 2005 and 2007, 5 patients with emphysematous pancreatitis were admitted. The 5 male patients ranged in age from 50 to 77 years. Four required at least 1 week in the intensive care unit. All 5 cases of emphysematous pancreatitis went on to be treated successfully with nonoperative management. Furthermore, after a minimum of 1-year follow-up, they remain out of hospital and continue to do well. The data suggest that emphysematous pancreatitis may be a favorable subtype of severe pancreatitis. In well-selected patients, nonoperative management with aggressive antibiotic treatment and nutritional support may suffice [235].

Intrahepatic fluid collections

Peripancreatic fluid collection suggests the anatomical-clinical scenario of necrotizing acute pancreatitis. However, intrahepatic fluid collection is a rare occurrence with fewer than 30 cases being reported in the medical literature. It was described 2 cases of intrahepatic fluid collection in 2 patients with acute biliary pancreatitis and discussed the therapeutic possibilities. The patients were successfully treated with percutaneous US/CT guided

drainage. It was concluded that intrahepatic fluid collection in the course of acute biliary pancreatitis is a rare occurrence. The therapeutic approach is the same as that for pancreatic and peripancreatic fluid collections. In case of infection, the patient undergoes percutaneous US/CT guided drainage [236].

Endoscopic treatment

Necrosectomy is the gold standard treatment for infected pancreatic necrosis (IPN). A percutaneous and endoscopic approach has been accepted in selected cases. Endoscopic drainage (ED) of IPN can be performed by using transpapillary or transmural procedures, or a combination of both with or without endoscopic ultrasound. The aim of one study was to determine the indications, complications, success rate, and the importance of assessment of main pancreatic duct integrity by endoscopic retrograde pancreatography (ERP) in patients with IPN. Records of all patients who underwent endoscopic necrosectomy from 2002 to Decmber 2007 were reviewed. A total of 56 patients were included. ED was performed using daily transmural and transpapillary drainage. A diagnostic pancreatogram (ERP) to search for communications between the pancreatic duct and the collection were performed in all cases and in cases where communication existed. A pre-cut needle knife was used to puncture the cyst wall, aspirate the content and then enter at the cyst cavity (contrast was injected to ensure opacification of the cyst and subsequent drainage). Sphincterotomy catheter or balloons were used to enlarge and ensure a wide cystoenterostomy. All patients were followed with computerized tomography scans or ultrasound to ensure clinical resolution. Mean follow-up was 21 months.49/56 patients could be successfully treated. ED was successful in 49 patients (87 %) and in 3 (13 %) it failed. Mean follow-up was 21 months. During this period, there were 2 (11 %) pseudocyst recurrences and only 1 (5 %) recurrence of new episodes of pancreatic necrosis, and all were managed clinically and/or endoscopically. No mortality was related to the procedure [237].

It was described a case of successful endoscopic management of two pancreatic abscesses in a critically ill patient. CT scan showed two large abscesses. The first was bulging to the posterior wall of the stomach and another at the tail of the pancreas. An endoscopic retrograde cholangiopancreatography was performed. The pancreatic duct communicated with the abscess at the tail of the pancreas. The drainage of this abscess was done transpapillarily. Endoscopic cystogastrostomy was performed to treat the pancreatic abscess that bulged to the posterior gastric wall. A double nasocystic tube was placed for continuous lavage of the abscess. Pseudomonas aeruginosa was cultured and antibiotics were administered according to sensitivity tests. The clinical status returned gradually to normal. A follow-up CT scan 4 months later showed complete resolution of abscesses. It was concluded that endoscopic drainge of pancreatic abscesses may be the therapy of choice in such patients mainly because it does not prevent the chance of subsequent surgical intervention if needed [238].

Radiologic interventions

It has previously been reported that organ failure and mortality in necrotizing pancreatitis (NP) are not different between patients with infected and sterile necrosis. However, management of this disease has evolved to include image-guided percutaneous catheter drainage (PCD) to improve morbidity and mortality. A total of 689 consecutive patients treated for acute pancreatitis between 2001 and 2005, of whom 64 (9 %) had pancreatic necrosis documented on contrast-enhanced computed tomography was studied. In the 64 patients with documented necrotizing pancreatitis, overall mortality was 16 percent. Thirty-six patients (56 %) had organ failure according to the Atlanta classification. Compared with patients with sterile necrosis, those with infected necrosis did not have an increased prevalence of organ failure or increased need for intubation, pressors, or dialysis but had an

increased mortality. Mortality in patients treated conservatively was 1 of 29 (3 %); in those with PCD alone, 6 of 11 (55 %); in those with percutaneous catheter drainage and surgery, 2 of 17 (12 %); and in those with surgery alone, 1 of 7 (14 %). All patients treated with PCD alone had organ failure, whereas 10 (59%) of those with PCD and surgery had organ failure. It was concluded that the use of percutaneous catheter drainage did not improve the mortality of necrotizing pancreatitisamong patients with organ failure [239].

Quality of life after acute pancreatitis

To explore the quality of life in patients treated medically during the acute phase of pancreatitis as well as at 2 and 12 months after discharge from the hospital. Forty patients were studied. The etiology of the pancreatitis was biliary causes in 31 patients and non-biliary causes in 9; mild disease was present in 29 patients and severe disease in 11. Thirty patients completed the two surveys at 2 and 12 months after hospital discharge. The SF-12 and EORTC QLQ-C30 questionnaires were used for the purpose of the study. The two physical and mental component summaries of SF-12, all the domains of EORTC QLQ-C30 (except for physical functioning and cognitive functioning) and some symptom scales of EORTC QLQ-C30 (fatigue, nausea/vomiting, pain, and constipation) were significantly impaired during the acute phase of pancreatitis. There was a significant improvement in the SF-12 physical component summary, and global health, role functioning, social functioning, nausea/vomiting, pain, dyspnea, and financial difficulties (EORTC QLQ-C30) at 2 months after discharge as compared to the basal evaluation. Similar results were found after 12 months except for the mental component score at 12-month evaluation, which was significantly impaired in acute pancreatitis patients in comparison to the norms. The physical functioning of the EORTC QLQ-C30 at basal evaluation was significantly impaired in patients with severe pancreatitis in comparison to patients with mild pancreatitis. It was concluded that two different patterns can be recognized in the quality of life of patients with acute pancreatitis: physical impairment is immediately present followed by mental impairment which appears progressively in the follow-up period [240].

Experimental

The aim of one study was to study the effects of resveratrol on severe acute pancreatitis (SAP)-induced brain injury. Ninety-six male Sprague-Dawley rats were randomly divided into 4 equal groups: sham operation, SAP, resveratrol-treated, and dexamethasone-treated. Each group was evaluated at 3, 6, and 12 hours. Myelin basic protein and zonula occludens 1 levels of the resveratrol group were lower than the SAP group at all time points. The treated group had significantly improved pathologic brain, increase in Bcl-2 expression, and decrease in Bax and caspases-3 expressions compared with the SAP group. The authors concluded that degradation of zonula occludens 1 is involved in the pathophysiology of brain injury in SAP; myelin basic protein can be used as a marker of brain injury in SAP. The protective effect of resveratrol might be associated with the up-regulation of Bcl-2 and down-regulation of Bax and caspase-3 [241].

It was previously observed decreased histopathological severity of acute necrotizing pancreatitis by parenteral nutrition with n-3 fatty acids. Thus, it was now sequentially analyzed the impact of n-3 fatty acids on prostaglandin and leukotriene synthesis in necrotizing pancreatitis in 198 Sprague-Dawley rats (11 groups, n=18) who underwent intraductal glycodesoxycholat instillation and 6-hour cerulein infusion. Afterward, saline was infused in groups 2, 4, 6, 8, and 10, whereas groups 3, 5, 7, 9, and 11 received infusion rich in n-3 fatty acids. Animals were killed after 6 (group 1), 10 (groups 2 and 3), 14 (groups 4 and 5), 18 (groups 6 and 7), 22 (groups 8 and 9), and 26 hours (groups 10 and 11). The

pancreas was histopathologically examined, and the pancreatic eicosanoid metabolism (prostaglandin E2, prostaglandin F1-alpha [PGF1-alpha]], and leukotrienes) and lipid peroxidation (thiobarbituric acid-reactive substance, superoxide dismutase, and glutathione peroxidase) were analyzed. Between the 14th and 26th hours, histopathologic scores (edema, inflammation, bleeding, and necrosis) were reduced in the n-3 fatty acid group compared with the corresponding saline group. Pancreatic prostaglandin E2 and PGF1-alpha were decreased between the 10th and 18th hour by n-3 fatty acids; PGF1-alpha was reduced after 26 hours compared with the corresponding saline group. Lipid peroxidation was decreased by n-3 fatty acids after 14 hours (thiobarbituric acid-reactive substance); however, there was no difference concerning lipid peroxidation protective enzymes (glutathione peroxidase and superoxide dismutase). It was concluded that parenteral therapy with n-3 fatty acids decreased histopathologic severity in necrotizing pancreatitis in rats by early inhibition of prostaglandin (E2 and F1-alpha) synthesis and reduction of lipid peroxidation [242].

High-mobility group box 1

To investigate the effects of high-mobility group box 1 (HMGB1) A box in experimental severe acute pancreatitis (SAP) severe acute pancreatitis was induced by 20 percent l-arginine abdominal cavity injection in mice. The serum levels of HMGB1, amylase, lipase, and biochemical indicators were measured 24 and 48 hours after induction of SAP. The pathological changes of the pancreas, lung, kidney, and liver for both SAP group and treatment group were observed and compared, as well as survival rate and surviving time. A box significantly improved the elevation of the serum levels of HMGB1, amylase, lipase, and biochemical indicators in SAP. The pathological changes of pancreas and organ injury in treatment group were more alleviated than that in SAP group. The mice survival rate of the treatment group (67 %) was significantly higher than that of the SAP group (27 %). It was concluded that a box has remarkable protective effect against pancreatitis and associated organ injury; HMGB1 probably participates in the inflammatory reaction and organ injury of severe acute pancreatitis as a late-acting mediator of inflammation [243].

PAF-antagonists

Platelet-activating factor (PAF) is an important mediator of inflammation and postulated to be involved in the pathogenesis of acute pancreatitis. In one study, we evaluated the therapeutic effect of PAF antagonist WEB 2086 in acute experimental pancreatitis of graded severity in rats. According to a block design, 64 animals were randomly allocated to 8 groups. Severe necrotizing pancreatitis was induced by intraductal infusion of taurocholic acid (4 %, 0.4 mL), and the combination of glycodeoxycholic acid (10 mmol/L, 1.0 mL/kg, intraductal infusion) and cerulein (5 microg/kg per hour, intravenous) was applied to induce intermediate pancreatitis, or cerulein alone (5 microg/kg per hour, intravenous) to establish edematous pancreatitis. WEB 2086 was given 15 minutes after beginning the induction of pancreatitis. Pancreatic microcirculation was analyzed in vivo with an epiluminescent microscope. Histopathology was evaluated by a validated score. Trypsinogen-activating peptide and serum amylase were analyzed sequentially. WEB 2086 had no significant influence on the breakdown of microcirculation, leukocyte adherence, histopathological damage, and amylase levels in severe necrotizing pancreatitis, intermediate pancreatitis, and edematous pancreatitis. Only in intermediate pancreatitis was there a significant reduction of trypsinogen-activating peptide levels [244].

CHRONIC PANCREATITIS

Epidemiology and demography

China

A multicenter study was initiated by the Chinese Chronic Pancreatitis Study Group to determine the nature and magnitude of chronic pancreatitis in China. Twenty-two hospitals representing all 6 urban health care regions in China participated in the study. The survey covered a 10-year period from 1994 to 2004. Multiple logistic regression was used for analyses. Results: The analysis included 2008 patients (65 % were men, mean age, 49 years). Chronic pancreatitis prevalence increased yearly from 1996 to 2003: 3.08, 3.91, 5.28, 7.61, 10.43, 11.92, 12.84, and 13.52 per 100,000 inhabitants. Chronic pancreatitis etiologies were alcohol (35 %), biliary stones (34 %), hereditary (7 %), and idiopathic chronic pancreatitis (13 %). Clinical feature were pain (76 %), maldigestion (36 %), jaundice (13 %), and steatorrhea (7 %). Complications were pseudocyst (26 %), diabetes (22 %), bile duct strictures (13 %), and ascites (2 %). With regard to the diagnosis, the sensitivity and specificity of endoscopic ultrasonography and endoscopic retrograde cholangio-pancreatography were 88 and 93 percent, and 87 and 93 percent, respectively. Three hundred ninety-one patients (19 %) received endoscopic therapy. Surgery was performed in 239 patients (12 %). It was concluded that in China, the incidence of chronic pancreatitis is rising rapidly [245].

India

Tropical pancreatitis, an idiopathic chronic pancreatitis (ICP) with unique features, has been described in south and north India. It was investigated the clinical profile of ICP patients in north India. Detailed demographic data was recorded and hematological and biochemical investigations were performed on 155 patients that had been diagnosed with chronic pancreatitis. Ultrasonography and computed tomography were performed in all patients. Magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreato-graphy, glucose tolerance test and fecal fat studies were performed on some patients. Patients were divided in to early or lateonset ICP (before or after 35 years of age). ICP was reported in 41 percent of patients, followed by alcoholic chronic pancreatitis (38 %). The mean age of ICP patients was 33 years and the mean duration of symptoms at the time of presentation was 40 months. Pain was the dominant symptom in both early- (95 %) and late-onset (100 %) ICP; pseudocyst was the most common local complication. Diabetes was observed in 17 percent of patients with early-onset ICP and 35 percent with late-onset ICP. Pancreatic calcification was noted in 46 percent of patients with early-onset and 48 percent with late-onset ICP. Pseudocyst and segmental portal hypertension occurred more frequently in non-calcific ICP whereas diabetes mellitus and abnormal fecal fat excretion occurred more frequently in patients with calcific ICP. It was concluded that ICP of north India appears to be different from classical tropical pancreatitis described in the literature and is associated with a higher prevalence of pain, lower frequencies of diabetes, calcification and intraductal calculi [246].

Risk of cancer

It was monitored 223 patients with chronic pancreatitis on a systematic basis from 1992 to 2005. During this 14-year period, we monitored the number of cigarettes smoked per year in addition to standard parametres measured by biochemical methods, endosonography, CT and ERCP exams, and assigned the alcoholic form of chronic pancreatitis to patients consuming more than 80g of alcohol per day on a systematic basis for more than 5 years in

the case of men, and 50 g of alcohol per day in the case of women, and classed the patients according the TIGARO classification. Alcoholic etiology was proven in 73 percent of the examined patients, chronic obstructive form of pancreatitis was diagnosed in 22 percent of patients, and only 5 percent of patients were classified into the idiopathic pancreatitis group. Pancreatic carcinoma in the region of chronic pancreatitis was found in 13 patients (6 %); stomach carcinoma was diagnosed in 3 patients with chronic pancreatitis, and oesophageal carcinoma in 1 patient of the total of patients monitored. Malignant pancreatic disease was diagnosed primarily in patients with alcoholic pancreatitis (5 %). During the period of 14 years, 11 patients died, 8 of the deaths being associated with pancreatic carcinoma. It was concluded that both pancreatic and extrapancreatic carcinoma in gastrointestinal location is a serious complication of protracted chronic, non-hereditary pancreatitis. Systematic identification and treatment of patients with chronic pancreatitis is therefore necessary for timely diagnosis of gastrointestinal and pancreatic malignancies [247].

Genetics

CFTR

DNA analyses of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in Japanese patients with idiopathic chronic pancreatitis (ICP) were performed to determine the relationship between the CFTR mutation and ICP. The study included patients with alcoholic pancreatitis (n = 20), patients with ICP (n = 20) and healthy volunteers (controls; n=110). The poly-T region in intron 8 of the CFTR gene was analysed by direct sequencing. The CFTR coding region was screened using single-strand conformational polymorphism and direct sequencing. In the controls, frequencies of the 5T genotype and 5T allele were 4.5 and 3.6 percent, respectively. The frequency of the 5T genotype was significantly higher in the ICP group (20 %) versus controls, but was not significantly different in alcoholic chronic pancreatitis patients (5 %). Thus, the CFTR gene mutation, especially the 5T genotype, appears to have some relationship to ICP prevalence in Japanese patients independent of cystic fibrosis [248].

Chymotrypsin C

Variations and haplotypes of the chymotrypsin C (CTRC) gene in Chinese patients with chronic pancreatitis and control subjects with genotype-phenotype correlation were investigated. One hundred and twenty-six patients with chronic pancreatitis were analyzed. The entire sequence of coding regions of exons 2, 3 and 7 and their neighboring intronic regions in introns 1, 2 and 6 of the CTRC gene were analyzed using PCR sequence-specific primers and direct sequencing. The exonic region of exon 7 and the neighboring intronic region of intron 6 were also analyzed in 90 geographically matched healthy control subjects. In total, 4 novel variations were identified in exons 2, 3 and 7 in 3 CP patients. A total of 2.3 percent (3/126) of our chronic pancreatitis patients carried variations of the CTRC gene. It was also first identified six new intronic variations in intron 6 which had not been reported before. The GAGGGG, GAGGAG and GAGTAG haplotypes assembled by six locus intronic variations c.640-41/c.640-40/c.640-39/c.640-37/c.640-36/c.640-35 in intron 6 were associated with a significantly higher susceptibility risk of CP (OR 66.75, 37.00, and 9.37, respectively). Novel CTRC gene variations and haplotypes are associated with CP in a Chinese population [249].

Spain

Mutations in the PRSS1 and the SPINK1 genes have variably been associated with alcohol-related, idiopathic and hereditary chronic pancreatitis. The aim of one study was to determine

for the first time the significance of PRSS1, SPINK1 mutations and genetic variants of AAT in a group of Spanish patients with chronic pancreatitis. One hundred and four consecutive patients with chronic pancreatitis were included, as well as 84 healthy control subjects. The R122H and N29I mutations in the PRSS1 gene, the N34S mutation in the SPINK1 gene and PiS and PiZ mutations in the AAT gene were analyzed by RFLP-PCR methods. No R122H mutation was found in the PRSS1 gene, and N29I mutation was detected in 8 percent of chronic pancreatitis patients. A N29I mutation was observed in 4 percent of patients with alcohol-related pancreatitis. A total of 6 percent of chronic pancreatitis patients were identified with the N34S mutation. Genotype MS, SS and MZ were detected in 18.3, 3.8 and 1.3 percent of patients, respectively. It was concluded that the percentage of N29I mutations in alcohol-related pancreatitis patients was higher than that reported in other studies, while the percentage of N34S and AAT mutations in alcohol-related pancreatitis and idiopathic chronic pancreatitis patients was similar [250].

Possible etiological factors

Chronic pancreatitis is an inflammatory disease followed by structural alterations – inflammation, fibrosis and acinar atrophy – pain emergence, exocrine and endocrine pancreatic insufficiency, severe alteration of quality of life. The pathogenetic mechanisms characteristic to this disease are not thoroughly known, but the identification of some genetic and autoimmune factors in certain entities has elucidated several pathogenetic links. The etiologic risk factors for chronic pancreatitis may associate each other and may cause different evolutions to the disease. By tracing out the risk factors and their typical working mechanisms, further pathogenetic treatments may occur, taking place precociously and preventing the evolution of the disease towards exocrine and endocrine pancreatic insufficiency [251].

Homocysteinemia

Homocysteine has been implicated in vascular dysfunction and thrombosis, as well as inflammatory conditions. One study was aimed to find out whether chronic pancreatitis is associated with hyperhomocysteinemia and derangements of transmethylation and transsulfuration pathways. It was estimated homocysteine and its metabolites in 45 alcoholic chronic pancreatitis patients, 45 tropical chronic pancreatitis patients, and 48 healthy controls. Significant increases in plasma total homocysteine and decreases in red blood cell folate, reduced glutathione, plasma methionine, cysteine, and urinary inorganic sulfate/creatinine ratio were observed in both alcoholic and tropical chronic pancreatitis patients in comparison with healthy controls. Red blood cell glutathione and plasma cysteine levels were significantly lower in alcoholic than in tropical chronic pancreatitis patients. However, plasma vitamin B12 levels were comparable between chronic pancreatitis patients and controls. No significant differences in these parameters were observed between diabetic patients and nondiabetic patients. Multivariate regression analysis showed a significant negative correlation between homocysteine and folate and a positive correlation between glutathione and cysteine levels. It was concluded that pancreatitis is associated with hyperhomocysteinemia and derangements in transmethylation and transsulfuration pathways. Low folate levels observed in these patients seem to have a key role in this derangement [252].

Changes in neurohormones

It was measured content of neuromediators (acetylcholine, serotonin) and gastrointestinal hormones (cholecystokinine and secretin) in the blood serum of patients with chronic pancreatitis to study protective properties of the mucus in the duodenum. In alcoholic

pancreatitis patients the response of biologically active substrates to standard meal changed: serotonin concentration rose from 0.40 ± 0.07 to 0.55 ± 0.05 mcg/ml (a statistically significant difference) while acetylcholin dropped from 1.7 ± 0.3 to 1.6 ± 0.3 mmol/l (not statistically significant). Biliary pancreatitis patients responded to the standard meal with a significant serotonin concentration rise from 0.28 ± 0.04 to 0.43 ± 0.05 mcg/ml, acetylcholin changed insignificantly from 1.5 ± 0.12 to 1.45 ± 0.21 mmol/l, respectively. CCK after standard meal significantly rose both in both types of patients, and both types had strong direct correlation between concentrations of serotonin and CCK and weak negative correlation with acetylcholin level. Reduction of secretin secretion diminished secretion of bicarbonates and mucus with simultaneous change in the quality of mucous gel. It was concluded that in chronic pancreatitis of various etiology there are changes in the level and proportions of neuromediators and hormones causing alterations in the regulation system. These disorders correlate with disturbances in pancreatic excretory function and destructive tissue changes. Bicarbonates secretion decreases and changes quality of the secreted mucus [253].

Amino acids

The circulating amino acid levels were determined in 12 patients with chronic pancreatitis, 12 pancreatic cancer patients, and 12 controls. Total amino acid concentrations were 2850 ± 71 micromol/L in controls, 2640 ± 96 micromol/L in chronic pancreatitis patients, and 2210 ± 123 micromol/L in cancer patients, which was statistically significantly different. In chronic pancreatitis patients, significant reductions in the concentrations of citrulline, gamma-aminobutyric acid, taurine, and aspartic acid were found, whereas in pancreatic cancer patients, the levels of phosphoethanolamine, gamma-aminobutyric acid, aspartic acid, taurine, arginine, threonine, alanine, citrulline, and tryptophan were reduced. There was a significant inverse relationship between the total amino acid levels and the white blood cell counts. The mechanisms underlying these defects may involve intestinal malabsorption as well as systemic inflammation. Providing selective amino acid supplementation to such patients may minimize the excess morbidity and mortality associated with protein malnutrition [254].

Diagnostics

Symptoms

Pancreatic panniculitis is rare form of panniculitis with associated pancreatic disease. The skin manifestations can occur at any time of the pancreatic pathology. It was now reported a case of pancreatic panniculitis associated with underlying chronic pancreatitis. The patient presented with painful subcutaneous nodules and the histology revealed the characteristic features of pancreatic panniculitis [255].

Endocopic ultrasography (EUS)

To provide histologic correlation of endoscopic ultrasound (EUS) findings believed to represent chronic pancreatitis 18 postmortem pancreatic specimens in patients dying of all causes were examined in vitro by EUS for features of chronic pancreatitis: echogenic foci, hypoechoic foci, echogenic main pancreatic duct (MPD), accentuated lobular pattern, cysts, irregular MPD, dilated MPD, side branch dilation, and calculi. The pancreata were then examined by two pathologists (blinded to the EUS/clinical findings) for histopathologic features of chronic pancreatitis. Six specimens were autolyzed, and in 1 specimen, MPD could not be seen by EUS. In the other 11 patients, 10 had evidence of chronic pancreatitis by EUS (>3 features) and by histopathologic examination (>2 features). One patient did not have chronic pancreatitis by either EUS or histologic examination. It was concluded that

endoscopic ultrasound accurately detected chronic pancreatitis, when compared with histopathologic examination. The presence of 3 or more features of chronic pancreatitis correlates with the histologic diagnosis of chronic pancreatitis, however, up to 3 features are frequently present in elderly patients dying of all causes [256].

The endoscopic ultrasound (EUS) diagnosis of chronic pancreatitis relies on the presence of up to nine distinct pancreatic parenchymal and ductal abnormalities, without considering other factors such as age, duration of disease or clinical symptoms. The goal of one study was to examine the impact of patient symptoms on EUS findings in patients with chronic pancreatitis. All patients with previously suspected chronic pancreatitis who had symptomatic disease referred to a medical center for pancreatic EUS were identified. Patients were stratified into two groups based on their clinical symptoms – pain only and steatorrhea ± pain. Groups were compared using two-tailed comparative testing. Fifty-three patients (group 1) with pain only and 27 patients with steatorrhea ± pain (group 2) were identified. Patients in group 1 were younger and more likely female. Compared to group 1 (pain only), group 2 (steatorrhea ± pain) had significantly more total (5.4 vs 3.3) and ductal abnormalities (2.6 vs 0.8), although the number of parenchymal abnormalities between groups 1 and 2 was not different. The presence of steatorrhea ± pain in patients with chronic pancreatitis undergoing pancreatic EUS examination is associated with more total and ductal abnormalities. Stratification based on underlying patient symptoms may be valuable as an adjunct to endosonographic findings in making or excluding the diagnosis of chronic pancreatitis [258].

ERCP in children

To evaluate indications, findings, therapies, safety, and technical success of endoscopic retrograde cholangiopancreatography (ERCP) in children of a Children's Hospital in Amsterdam, the Netherlands a retrospective analysis by medical records was done. Success was defined as obtaining accurate diagnostic information or succeeding in endoscopic therapy. Sixty-one children (age 3 days to 17 years, mean age 7 years) underwent a total of 99 ERCPs. Of those patients, 51 percent (31/61) were younger than 1 year, 84 percent had biliary indications, and 16 percent had pancreatic indications for the performance of ERCP. The complication rate was 4 percent (4/99) and included substantial pancreatitis and mild irritated pancreas. No complications occurred in children younger than 1 year. Indications for ERCP are different for children and adults. A laparotomy could be prevented in 12 percent of children with suspicion of biliary atresia [259].

Breath tests

Although the fecal elastase-1 test is a satisfactory pancreatic exocrine function test, breath tests that use stable isotopes have been developed recently as alternatives. We evaluated the usefulness of a ^{13}C-labeled mixed triglyceride breath test for assessing pancreatic exocrine function after pancreatic surgery. The breath test and the fecal elastase-1 test were performed on 7 healthy volunteers, 10 patients with chronic pancreatitis, and 95 patients after pancreatic surgery. The breath test was analyzed with isotope ratio mass spectrometry and the cumulative recovery of $^{13}CO_2$ at 7 hours (% dose ^{13}C cum 7h) was calculated. The fecal elastase-1 concentration was determined immunoenzymatically. Both the fecal elastase-1 concentration and the % dose ^{13}C cum 7h of chronic pancreatitis patients and pancreatic resection patients were less than those of healthy volunteers. In all subjects, % dose ^{13}C cum 7h correlated with the fecal elastase-1 concentration. Accuracy rates for clinical symptoms, including clinical steatorrhea, for the fecal test and the breath test were 62 and 88 percent, respectively. It was concluded that the ^{13}C-labeled mixed triglyceride breath test might be more useful than the fecal elastase-1 test for evaluating pancreatic exocrine function after pancreatic resection [260].

Association with liver disease

Although chronic pancreatitis and liver cirrhosis are common sequelae of excess alcohol consumption, the two conditions are rarely associated. It was studied the prevalence of simultaneous liver cirrhosis and chronic pancreatitis by post-mortem autopsy data from 620 individuals with a history of excess alcohol consumption and 100 non-alcoholics (controls). The individuals were classified into groups based on macroscopic observations of pancreas (no injury, acute pancreatitis, fibrosis and chronic pancreatitis) and liver (no injury, moderate steatosis, severe steatosis, and cirrhosis). The same classification system was used for histological data, which was used to confirm and correlate macroscopic results. Out of the 183 patients with liver cirrhosis, 33 (18 %) had chronic pancreatitis and 93 (51 %) pancreatic fibrosis. Out of the 230 patients with severe steatosis, 37 (16 %) had chronic pancreatitis and 97 (42 %) were found to have a pancreatic fibrosis. Thirty-three (39 %) with chronic pancreatitis also showed liver cirrhosis and 37 (44 %) severe steatosis. Thirty-eight percent of the patients with a pancreatic fibrosis were found to have also liver cirrhosis and in another 40 percent severe steatosis. Thirty-five patients showed neither hepatic nor pancreatic injury. It was found no chronic pancreatitis or liver cirrhosis in the control group (n=100). It was concluded that contrary to common believe there is a close association between pancreatic and hepatic injury in patients with increased alcohol consumption, and the degree of organ damage between the two organs correlate [261].

Alcohol-induced chronic pancreatitis

Chronic pancreatitis is a progressive inflammatory condition characterized by repeated attacks of abdominal pain, and the destruction and fibrosis of the pancreatic parenchyma which causes to reduced exocrine and endocrine functions. Alcohol is the most common cause of chronic pancreatitis. Although abstinence is usually considered a prerequisite for successful treatment of alcoholic chronic pancreatitis, one often encounter patients who have repeated attacks from the compensated stage through the transitional stage. In alcoholic chronic pancreatitis, continued alcohol consumption causes changes in the digestive hormones and vagal nerve function that induce the pancreatic acinar cells to oversecrete protein, increasing the protein concentration and viscosity of the pancreatic juice. This induces protein sedimentation from the pancreatic juice and formation of protein plugs within the pancreatic duct, triggering repeated attacks of acute pancreatitis. The treatment of alcoholic chronic pancreatitis includes alleviation of symptoms, particularly abdominal pain, elimination of trigger factors, prevention of recurrence and disease progression, adjuvant therapies for pancreatic exocrine and endocrine failure. Recently, the main constituent proteins in these protein plugs have been identified, enabling trials of several therapies, such as the administration of secretin formulations and endoscopic removal. Bromhexine hydrochloride, a bronchial mucolytic, has an affinity for the pancreatic acinar cells, inducing them to secrete pancreatic juice of low viscosity. In one review, it was summarized the most recent thoughts about alcoholic chronic pancreatitis, and the new treatments, and in particular, it was presented our findings concerning the efficacy of bromhexine hydrochloride in the treatment of this disease [262].

Seventy percent of pancreatitis cases are considered to be induced by alcohol in Finland. Half of those fallen ill with alcohol-induced acute pancreatitis will have relapses. A prospective follow-up study showed that the level of dependence on alcohol constitutes the most important risk factor. Continued drinking was shown to be a dose-responsive risk factor for relapse; abstinence provided for a complete protection against renewed pancreatitis. In a randomized study, a semi-annual meeting with a healthcare professional specialized in substance abuse problems significantly reduced new episodes of acute pancreatitis. It is thus

possible to at least reduce relapses by intervening in the risk factors [263].

Groove pancreatitis

Groove pancreatitis is an uncommon form of focal chronic pancreatitis that involves the duodenal wall or "groove" area (between the pancreas, common bile duct, and duodenum). It remains largely an unfamiliar entity to most physicians and is often misdiagnosed as pancreatic malignancy or autoimmune pancreatitis because of its "pseudotumor" formation. In one case series, it was presented four cases of groove pancreatitis which highlight important clinical aspects of this disease entity [264].

Pain

Theories on investigations of pain in patients with chronic pancreatitis

A total pancreatectomy for pain relief in chronic pancreatitis has been proposed as ultima ratio, but the rationale for such a mutilating option has not been defined, and the discussion on indication, results, and outcome of this procedure remains contradictory. There are several major problems why series of chronic pancreatitis from different centers regarding success of therapeutic interventions are not comparable. In particular, the pathomechanism of pain in chronic pancreatitis is poorly understood; there is no generally accepted pain score system, and in most series, nature and cause of pain are not adequately documented. Moreover, reliable data on the long-term pain profile of chronic pancreatitis should be based on prospective studies of mixed medical-surgical series of chronic pancreatitis of various etiology, primarily because data of surgical series are biased excluding approximately 50 percent of chronic pancreatitis patients who never required surgical intervention for pain relief [265].

Types of pain

Abdominal pain in chronic pancreatitis is difficult to treat and appropriate choice of treatment is controversial. It has been suggested that patients with chronic pancreatitis particularly from alcohol (ACP) with intermittent attack of abdominal pain (type A pain) should be managed conservatively because pain relief will be achieved in most cases. Data of all patients with chronic pancreatitis with type A pain, who were followed-up and managed conservatively during 2004-2008 were analyzed. Pain relief was defined by the absence of abdominal pain for more than 1 year. Twenty-two patients were followed-up with a median duration of 31 months (range 5-96 months). The etiology of chronic pancreatitis was alcoholic (ACP) in 12 (56 %), early-onset idiopathic (E-ICP) in 5 (22 %) and late-onset idiopathic (L-ICP) in 5 (22 %). Alcohol abstinence was successful in every ACP patient. Overall, 18 patients (82 %) had pain relief with a median duration of 39 months (range 16-167 months) from the onset of pain or 14 months (range 11-57 months) from the time of diagnosis of chronic pancreatitis. Pain relief was achieved at a higher level mainly in ACP (100 %) and L-ICP (80 %) but was only 40 % in E-ICP Median duration from onset until pain relief were 28 months (range 16-167 months) for ACP, 36 months (range 16-39 months) for L-ICP and 120 months (range 42-120 months) for E-ICP. The difference was statistically significant between L-ICP and E-ICP, but not between ACP and E-ICP and not between ACP and L-ICP. Median duration from the time of diagnosis of chronic pancreatitis until pain relief was only 14 months for ACP 13 months for L-ICP but was 52 months for E-ICP. None of the patients required narcotics, endoscopic therapy or surgery. The authors concluded that conservative management was feasible and effective in most patients with chronic pancreatitis and type A pain, particularly ACP after alcohol abstinence, and L-ICP Conservative treatment was not effective in E-ICP

[266].

The chemokine fractalkine induces migration of inflammatory cells into inflamed tissues, thereby aggravating inflammatory tissue damage and fibrosis. Furthermore, fractalkine increases neuropathic pain through glial activation, which can be diminished by blocking of its receptor, CX3CR1, through neutralizing antibodies. As chronic pancreatitis is characterized by tissue infiltration of inflammatory cells, fibrosis, pancreatic neuritis and severe pain, the roles of fractalkine and CX3CR1 were investigated in CP (n=61) and normal pancreas (NP, n=21) by QRT-PCR, western blot and immunohistochemistry analyses. Their expression correlated with the severity of pancreatic neuritis, fibrosis, intrapancreatic nerve fiber density and hypertrophy, pain, CP duration and with the amount of inflammatory cell infiltrate immuno-positive for CD45 and CD68. Advanced fibrosis was associated with increased fractalkine expression, whereas in vitro fractalkine had no significant impact on collagen-1 and alpha-SMA expressions in hPSCs. Therefore, pancreatic fractalkine expression appears to be linked to visceral pain and to the recruitment of inflammatory cells into the pancreatic tissue and nerve fibers, with subsequent pancreatic neuritis. However, pancreatic fibrogenesis is probably indirectly influenced by fractalkine. Taken together, these novel findings suggest that CX3CR1 represents a potential novel therapeutic target to reduce inflammation and modulate pain in chronic pancreatitis [267].

Medical pain treatment

The aim of one study was to evaluate the efficacy of intrathecal narcotics pump (ITNP) as an alternative treatment for patients with pain from chronic pancreatitis. ITNP offers the advantages of reversibility, lower total narcotic dose, and the pancreas remaining intact. Thirteen patients (8 female, 5 male), with mean age 41 years, who had experienced intractable upper abdominal pain from chronic pancreatitis were reviewed. Each patient had multiple other failed treatment modalities, including partial pancreatic resection (n=6). They were offered ITNP after a successful intraspinal opioid trial. Etiologies of the pancreatitis included idiopathy (n=3), cystic fibrosis (n=2), alcohol (n=2), and pancreas divisum (n=6). The median duration of severe, intractable pain prior to ITNP was 6 years (2-22 years). The median follow-up time after ITNP was 29 months (range, 7-94 months). The ITNP was in situ for a mean duration of 29 months (range, 0.5-94 months). Seven patients had pump exchange or removal for various reasons; improvement of pain at month 53 (n=1), meningitis (n=1), meningitis with subsequent replacement (n=1), pump failure at month 31, 68, 79, and 84 (n=4). There were no deaths. The mean pain score prior to implantation was significantly higher than 1 year after and last follow-up. The median oral narcotic dose before and 1 year after ITNP were morphine sulfate equivalents 338 mg per day (range, 68-1320) and 40 mg per day (range, 0-1680), respectively. Two patients were considered failures, as they still require a high dosage of both oral and intrathecal medications to control their pain, despite significant pain-score improvement. One patient who was excluded due to meningitis was also considered a failure. Therefore, the overall success rate of ITNP based on an intention-to-treat analysis was 77 percent (10/13). The major complications of ITNP were central nervous system infection requiring pump removal (n=1), cerebrospinal fluid leak requiring laminectomy (n=1), and perispinal abscess with bacterial meningitis requiring pump removal (n=1) [268].

Pancreatic enzymes as treatment for pain

The multiple possible etiologies of painful chronic pancreatitis combined with the likelihood that many patients with the condition are addicted to alcohol (and possibly continue to abuse alcohol) make clinical research in this field particularly challenging. Additionally, the biologic basis of pain in chronic pancreatitis remains somewhat controversial. Multiple other

etiologies have been proposed and are reviewed elsewhere; some experts have even postulated that pain in chronic pancreatitis may actually be centrally mediated, rather than mediated by inflammation of the pancreas itself. It has been proposed that administering supplemental porcine pancreatic extracts to patients with painful chronic pancreatitis stimulates receptors in the proximal small intestine and triggers a negative-feedback loop which suppresses baseline pancreatic enzyme secretion, decreasing ductal pressures, thereby decreasing pain. Many patients receive a therapeutic trial of pancreatic enzyme supplementation at some point in the course of their disease, but it is unclear what the expected outcome of such a trial should be and whether or not all patients should receive a trial of pancreatic enzymes. It should be noted, however, that other proposed pathophysiological mechanisms for pain exist, including chronic perineural inflammation and fibrosis, uninhibited cholinergic stimulation of pancreatic secretion and colonic hypermotility due to malabsorption and steatorrhea. Of these alternative proposed etiologies, only colonic hypermotility due to steatorrhea and malabsorption would potentially respond to pancreatic enzyme supplementation. It was searched PubMed for all studies of pancreatic enzyme supplementation for painful chronic pancreatitis from 1980 to 2009. In 1998, a technical review published by the American Gastroenterological Association (AGA) found that “the role of pancreatic enzymes in reducing pain in chronic pancreatitis … remains unclear”. However, an AGA medical position statement appearing in the same issue of Gastroenterology recommended routine use of pancreatic enzyme supplements for painful chronic pancreatitis. The AGA medical position statement does advocate the routine use of a quality-of-life (QOL) questionnaire though the AGA makes no specific recommendation as to which one. Nine studies (6 articles and 3 abstracts) of pancreatic enzyme supplementation for the treatment of pain in chronic pancreatitis have been undertaken or reported, with widely varying results. The published clinical trials of enzyme replacement for pain relief in painful chronic pancreatitis are plagued by a number of methodological and design flaws. These include, but are not limited to, lack of a priori power analysis, failure to use validated instruments to assess pain or health-related quality of life, use of crossover designs, selection of study populations which are not generalizable to clinical patient populations, and use of coated pancreatic enzymes rather than uncoated forms (only 2 studies have evaluated uncoated enzymes). Five of the studies noted no improvement in pain with treatment, but all failed to report whether an a priori power analysis was done, raising the possibility of type 2 error – sufficient numbers of patients may not have been studied to detect a significant difference. Further, even though 4 of the 9 published studies reported improvement in pain (statistically significant p-values) with pancreatic enzyme supplements, they also failed to report having done an a priori power analysis. All studies reported significant placebo responses. Failure to use validated instruments or to systematically assess health-related quality of life (HRQOL) is another common problem with the published studies. Only 2 of the 9 studies assessed HRQOL in a systematic fashion, using published, validated instruments. Seven of the 9 published clinical trials also made use of crossover designs. Crossover designs are beneficial in reducing confounding because each patient serves as his own control and they reduce the required number of participants. However, numerous problems exist with crossover designs – carryover effects, assignment sequence, and dropouts in particular. Finally, selection of patients in the published studies is nonuniform and is poorly described, particularly with regard to rigorous screening for alcohol abuse, a potential confounder. One of the most important issues in the treatment of patients with painful and nonpainful chronic pancreatitis is alcohol abstinence. Achieving alcohol abstinence is difficult in the best circumstances and may be made more complicated by a chronic pain condition such as painful chronic pancreatitis. What is not clear, however, is what to do with patients who continue to abuse alcohol or relapse during treatment. It is clear that the current published studies have not definitively answered the question of whether or not pancreatic enzyme supplementation is useful in painful chronic pancreatitis. Based upon the published studies, the authors would recommend that clinicians follow the general guidelines proposed by the AGA. They would, however, add the following caveats for the use of pancreatic enzymes in painful chronic pancreatitis [269]:

- pain should be assessed in a standardized and repeatable fashion prior to initiating a therapeutic trial of pancreatic enzymes. This could be as simple as using a 10-cm visual-analog pain scale which is widely available and takes just seconds for a patient to fill out
- therapeutic trials should be limited in time to 6 weeks with uncoated enzymes and concurrent acid suppression, at which point another standardized pain measurement questionnaire should be filled out
- if the clinician feels that narcotics should be a part of the pain management strategy for a patient, pill counts should be part of routine pain assessment at clinic visits
- alcohol rehabilitation should be considered for any patient with ongoing alcohol abuse – before beginning therapy with enzyme supplements
- since only one study has shown significant reductions in pain with coated pancreatic enzymes they would not recommend their use in painful chronic pancreatitis in general

Safety of pancreatic enzyme supplementation

To evaluate the efficacy and safety of a pancreatic enzyme preparation specifically developed for infants and small children with cystic fibrosis (CF) 12 patients with CF younger than 24 months with pancreatic exocrine insufficiency and a coefficient of fat absorption (CFA) less than 70 percent were treated with Creon for Children (Solvay Pharmaceuticals GmbH, Hannover, Germany) minimicrospheres for 8 weeks. The primary end point was the mean change from baseline in the CFA after 2 weeks of treatment, based on 72-hour fat balance assessments. Two weeks' treatment with Creon for Children resulted in a significant increase in the mean CFA from 58 percent at baseline to 85 percent in the full analysis sample. There was a significant reduction of mean stool fat and mean fecal energy loss at 2 weeks. Dietary fat intake did not change, whereas an improvement was observed in stool frequency and characteristics. Patient weight and height increased over 8 weeks of treatment. No serious adverse event was reported [270].

Surgical interventions

Outcome of pancreatoduodenectomy

Pancreatic resection can be performed to ameliorate the sequelae of chronic pancreatitis in selected patients. The perceived risk of pancreatectomy may limit its use. Using a national database, this study compared mortality after pancreatic resections for chronic pancreatitis with those performed for neoplasm. Patient discharges with chronic pancreatitis or pancreatic neoplasm were queried from the Nationwide Inpatient Sample, 1998 to 2006. To account for the Nationwide Inpatient Sample weighting schema, design-adjusted analyses were used. There were 11,048 pancreatic resections. Malignant neoplasms represented 64 percent of the sample; benign neoplasms and pancreatitis comprised 17 percent and 19 percent, respectively. In-hospital mortality rates were 2.2 percent and 1.7 percent for the pancreatitis and benign tumor cohorts, respectively, compared with 5.9 percent for the malignancy cohort, which was a significant difference. A multivariable logistic regression examined differences in mortality among diagnoses while adjusting for patient and hospital characteristics; covariates included patient gender, race, age, comorbidities, type of pancreatectomy, payor, hospital teaching status, hospital size, and hospital volume. After adjustment, patients undergoing resection for pancreatitis were at a significantly lower risk of in-hospital mortality when compared with those with malignant neoplasm (odds ratio, 0.43; 95 % confidence interval 0.28 to 0.67). Pancreatectomies for chronic pancreatitis have lower in-hospital mortality than those performed for malignancy and similar rates as resection for benign tumors. Pancreatic resection, which can improve quality of life in chronic pancreatitis

patients, can be performed with moderate mortality rates and should be considered in appropriate patients [271].

Pancreatogastrostomy

Pancreaticogastrostomy is a less used operation for drainage. In one series pancreaticogastrostomy was done in 37 patients with dilated ducts during the period from 2002-2008. Anastomosis of the pancreas to the posterior wall of stomach was performed using pancreatic duct to gastric mucosa technique. The cases were followed up and it was seen that pancreaticogastrostomy was an effective operation for chronic pancreatitis. Most patients (89 %) got relieved of pain for first several years. It is also a less time taking procedure to perform as no Roux-en-y construction is needed [272].

Longitudinal pancreatodjejunostomy

Obstruction of the main pancreatic duct in chronic pancreatitis (CP) leads to an increased intraductal and intraparenchymal pressure causing pain. In one study it was evaluated the outcome of surgical treatment of CP including the quality of life following Partington-Rochelle pancreaticojejunostomy performed for intractable pain. Between 2002 and 2008, PRP the method was performed in 17 patients in whom the diameter of the main pancreatic duct exceeded 7 mm and there was no inflammatory tumor in the pancreatic head. Perioperative morbidity and mortality were analyzed in all patients. The long term outcome including the quality of life (Karnofsky index) was evaluated in 9 patients who were followed with a mean 28 (range 13-60) months since surgery. Complications in the postoperative period were found in 3 (18 %) patients including 1 death due to a myocardial infarction shortly after surgery. All patients submitted to the long-term evaluation reported a significant pain reduction by an average of 6 (5-8) points in a 10-points visual analogue scale. The Karnofsky index increased significantly from a mean 52 percent (40-70 %) before surgery up to 82 percent (70-90 %) following surgery and long-term [273].

Islet transplantation

Transplantation of the whole pancreas or islet of Langerhans transplantation are alternatives to intensive insulin treatment, which decreases long-term complications at the cost of an increase of severe hyoglycemia. Pancreas transplantation, indicated mainly to diabetic patients with simultaneous kidney transplantation, has a high success rate, but is accompanied by high morbidity due to general surgery. Islet transplantation, a cell-therapy for type 1 diabetes, is in full development. It is mainly indicated as islet transplant alone in patients suffering from brittle diabetes, and is associated with a very low risk due to minimally invasive technique, but a lower rate of long-term success. New potential sources of beta cell replacement are beta-cell lines, stem cells and xenotransplantation [274].

Intraportal autotransplantation

The probability of insulin independence after intraportal islet autotransplantation (IAT) for chronic pancreatitis treated by total pancreatectomy 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) for patients with chronic pancreatitis undergoing total pancreatectomy and IAT. Eighteen pediatric chronic pancreatitis patients aged 5 to 18 years (median, 16 years) who underwent total pancreatectomy and 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 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 total pancreatectomy and intraportal autotransplantation 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 [275].

The only clinically acceptable radical treatment for patients with insulin-dependent diabetes mellitus is a whole pancreas transplantation, or alternatively an infusion of isolated islet cells into the hepatic portal venous system. Allogeneic transplantation of isolated islet cells is a procedure used only in a highly specific group of recipients, whereas intensive insulin treatment still remains the best therapy to achieve glycemia control in most patients with type 1 diabetes. Two groups of allograft recipients should be taken into consideration when scheduled for islet cell transplantation. The first group comprises allogeneic kidney recipients with a stabilized graft function for >6 months who receive chronic immunosuppression and require transplantation for end-stage renal disease caused by diabetic nephropathy. The second group consists of patients with unsatisfactory glycemic control despite insulin therapy, life-threatening hypoglycemic episodes and a rapid progression of long-term complications. Despite increasingly beneficial outcomes, islet cell transplantation has several limitations. Maintaining normoglycemia without exogenous insulin administration and appropriate selection of immunosuppressive agents to prolong graft survival are the major challenges. The aim of related studies has been to optimize all phases of islet cell transplantation in order to achieve total insulin independence and prolong graft survival [276].

Open islet cell transplantation
One study examined 85 consecutive patients undergoing total pancreatectomy (± islet cell transplant), examining pain relief, insulin requirements, and glycemic control postoperatively. A prospective database of all patients undergoing total pancreatectomy for chronic pancreatitis was used to record preoperative and postoperative details from 1996 to 2006. There were 3 postoperative deaths (1 islet recipient and 2 nonislet patients). The median number of acute admissions for pain fell from 5 to 2 after pancreatectomy, and the median length of stay from 6.2 days to 3.3 days. At 12 months postoperatively, the number of patients on regular opiate analgesia fell from 91 to 40 percent and by 5 years to 16 percent. There was a significant reduction in the patients' visual analogue pain score after surgery from 9.7 to 3.7. Five patients were insulin independent at 5 years. Median 24-hour insulin requirements were significantly lower in the islet group (16 vs 40 units at 5 years postoperatively). It was concluded that total pancreatectomy is effective in reducing pain and dependence on opioid analgesia in patients with chronic pancreatitis. The addition of an islet cell transplant results in a reduction in 24-hour insulin demands, as well as potentially achieving insulin independence [277].

Other interventions agains pain

Pancreatic duct stenting

Endoscopic therapy with pancreatic duct stenting in painful chronic pancreatitis is effective at reducing pain. Few studies have compared response to different pancreatic duct stent diameters. In one study, it was retrospectively analyzed the effect of pancreatic duct stent diameter on hospitalization for abdominal pain in chronic pancreatitis. An existing database was queried to identify individuals who received pancreatic duct stenting for chronic pancreatitis. Each patient was grouped according to stent diameter: (1) 8.5 F stents or smaller and (2) 10 F stents. The main outcome was number of hospitalizations adjusting for varying follow-up time and controlling for age, sex, and etiology of pancreatitis using a

negative binomial model. One hundred sixty-three patients underwent pancreatic duct stent placement for chronic pancreatitis from 1995 to 2007. One hundred twenty-nine patients (79 %) received predominantly pancreatic duct stents 8.5 F or smaller in diameter, and 34 patients (21 %) received predominantly pancreatic duct stents 10 F in diameter. There was no statistically significant difference in population characteristics between the two groups. The 10 F stent group had a statistically significant lower rate of hospitalization. It was concluded that patients who received larger diameter pancreatic duct stents had fewer hospitalizations for abdominal pain [278].

To assess the long-term outcomes of endoscopic minor papilla therapy in a spectrum of symptomatic patients with pancreas divisum patients with pancreas divisum coded in a prospective database as having had minor papilla endotherapy (1997-2003, n=145) were grouped into 3 categories: acute recurrent pancreatitis, chronic pancreatitis, and chronic/recurrent epigastric pain. Telephone follow-up was conducted (78 % of patients), including quesions regarding interval co-interventions and narcotic use. Primary success was defined as clinical improvement (better or cured on a Likert scale), without needing narcotics, after one therapeutic endoscopic retrograde cholangiopancreatography. Primary success rates in acute recurrent pancreatitis, chronic pancreatitis, and chronic/recurrent epigastric pain were achieved in 53, 18, and 41 percent, respectively; and secondary success rates (< 2 additional endoscopic retrograde cholangiopancreatographies), 71, 46, and 55 percent, respectively (median follow-up, 43 months; range, 14-116 months). Younger age and chronic pancreatitis independently predicted a lower chance of success. Significant long-term improvement can be achieved with endoscopic therapy in selected patients with pancreas divisum, although many require multiple procedures. Older patients, without chronic pancreatitis, were most likely to respond [279].

Endoscopic therapy with pancreatic duct stenting in painful chronic pancreatitis is effective at reducing pain. Few studies have compared response to different pancreatic duct stent diameters. In one study, it was retrospectively analyzed the effect of pancreatic duct stent diameter on hospitalization for abdominal pain in chronic pancreatitis. An existing database was queried to identify individuals who received pancreatic duct stenting for chronic pancreatitis. Each patient was grouped according to stent diameter: 8.5 F stents or smaller and 10 F stents. The main outcome was number of hospitalizations adjusting for varying follow-up time and controlling for age, sex, and etiology of pancreatitis using a negative binomial model. One hundred sixty-three patients underwent stent placement for chronic pancreatitis from 1995 to 2007. One hundred twenty-nine patients (79 %) received predominantly stents 8.5 F or smaller in diameter, and 34 patients (21 %) received predominantly stents 10 F in diameter. There was no statistically significant difference in population characteristics between the two groups. The 10 F stent group had a statistically significant lower rate of hospitalization. It was concluded that patients who received larger diameter pancreatic duct stents had fewer hospitalizations for abdominal pain [280].

Although the pathogenesis of pain is still poorly understood, an increase in intraductal pressure may be the dominant factor. The management of pain can involve medical, endoscopic, neurolytic, and surgical therapies. Endotherapy includes pancreatic sphincterotomy, extraction of stones, placement of stent, and dilatation of strictures, sometimes preceded or followed by extracorporeal shock-wave lithotripsy. Several studies have now shown that endotherapy provides partial or complete relief of pancreatic pain in a majority of patients with an acceptable frequency of early and late complications. Endotherapy should now graduate from an experimental form of treatment to a realistic treatment option in patients with chronic or relapsing pain, particularly in the setting of calcific chronic pancreatitis [281].

Proximal migration of pancreatic stents is a serious problem which can need the extensive surgery with following exo- and endocrine insufficiency. Therefore the possibility of

endoscopic solution of mentioned problem is very important. The purpose of one publication is presentation the case of proximal migration "pig tail" pancreatic stent and endoscopic technique removal it [282].

Plexus block

Endoscopic ultrasound (EUS)-guided celiac plexus block/neurolysis (CPB/N) can be performed by injecting at the base (central) or on either side (bilateral) of the celiac axis. Central CPB/N is easier and possibly safer. Bilateral CPB/N is more difficult but may be more effective as it reaches more ganglia. The aim of one study was to compare the short-term safety and efficacy of central and bilateral CPB/N. Central CPB/N was used in the first half of the study period and bilateral CPB/N in the last half. The primary outcome was the percent reduction in visual analog pain scores at day 7. A total of 184 patients were eligible. Out of them, 24 (13 %) were excluded for incomplete data. A total of 160 were left (71 central, 89 bilateral). The groups were similar for all cogent variables. Bilateral CPB/N was significantly more effective than central CPB/N (mean percent pain reduction 70 % (61-80) vs 46 % (33-57)). The only predictor of a >50 percent pain reduction was bilateral CPB/N (odds ratio 3.6, 1.7-7.3). Only one complication was noted: self-limited bleeding because of laceration of the adrenal artery following bilateral celiac plexus block in an anticoagulated patient [283].

Radiotherapy

It was reasoned that anti-inflammatory radiotherapy, which has proven useful to alleviate other painful inflammatory painful disorders, might prove valuable for severely symptomatic patients with chronic pancreatitis. It was prospectively studied the efficacy of single-dose anti-inflammatory radiotherapy in 15 consecutive patients with chronic pancreatitis who fulfilled the following criteria: either two flare-ups of pancreatitis in the previous 6 months and/or continuous pain for more than 3 months. Treatment consisted of a single radiation dose of 8 Gy to the pancreas. Exocrine function (fecal elastase), endocrine function (c peptide), quality of life (EuroQol questionnaire), and clinical outcome were assessed before and after radiation. Response was defined as no further pain or flare-ups of pancreatitis. During follow-up (median: 39 months; range: 4-72 months), 12 patients had no further pain or flare-ups. One patient required a second radiation dose 1 year after the initial treatment, but he has remained well ever since (50 months). Two other patients did not respond to radiotherapy. After radiotherapy either exocrine or endocrine pancreatic function, or both, deteriorated in three patients. Patients who responded to treatment (13/15) gained 4-20 kg in body weight during follow-up (median 4 kg) and EuroQol improved significantly from 0.58 to 0.86. It was concluded that radiotherapy for severe symptomatic chronic pancreatitis appears to be a useful and effective therapeutic choice that could potentially substitute for or delay surgery [284].

Halofunginol as prevention of fibrosis

Chronic pancreatitis is characterized by inflammation and fibrosis. It was evaluated the efficacy of halofuginone, an inhibitor of collagen synthesis and myofibroblast activation, in preventing cerulein-induced pancreas fibrosis. Collagen synthesis was evaluated by in situ hybridization and staining. Levels of prolyl 4-hydroxylase-beta (P4H-beta), cytoglobin/stellate cell activation-associated protein (Cygb/STAP), transgelin, tissue inhibitors of metalloproteinases, serum response factor, transforming growth factor-beta (TGF-beta), Smad3, and pancreatitis-associated protein 1 (PAP-1) were determined by immunohistochemistry. Metalloproteinase activity was evaluated by zymography. Halofuginone prevented cerulein-dependent increase in collagen synthesis, collagen cross-linking enzyme P4H-beta, Cygb/STAP, and tissue inhibitors of metalloproteinase 2.

Halofuginone did not affect TGF-beta levels in cerulein-treated mice but inhibited serum response factor synthesis and Smad3 phosphorylation. In culture, halofuginone inhibited pancreatic stellate cell proliferation and TGF-beta-dependent increase in Cygb/STAP and transgelin synthesis and metalloproteinase 2 activity. Halofuginone increased c-Jun N-terminal kinase phosphorylation in pancreatic stellate cells derived from cerulein-treated mice. Halofuginone prevented the increase in acinar cell proliferation and further increased the cerulein-dependent PAP-1 synthesis. It was concluded that halofuginone inhibits Smad3 phosphorylation and increases c-Jun N-terminal kinase phosphorylation, leading to the inhibition of pancreatic stellate cell activation and consequent prevention of fibrosis. Halofuginone increased the synthesis of PAP-1, which further reduces pancreas fibrosis. Thus, halofuginone might serve as a novel therapy for pancreas fibrosis [285].

Pancreatopleural fistulae

Pancreaticopleural fistula (PPF) is an unusual complication of chronic pancreatitis. Its diagnosis is obscured by predominance of pulmonary symptoms. A review of clinical presentation, etiology, diagnostic, and treatment modalities is presented in context of two cases from one institution. Case reports and case series of PPFs in the English literature from 1960 to 2007 were identified in the PubMed, OVID, and EMBASE search engines. Fifty-two cases of pancreaticopleural fistula were identified. Common presenting complaint was dyspnea (65 %) followed by abdominal pain (29 %), cough (27 %) and chest pain (23 %). Computed tomography scanning diagnosed PPF in 8 (47 %) of 17 patients, endoscopic retrograde cholangiopancreatography diagnosed PPF in 25 (78 %) of 32 patients, and magnetic resonance cholangiopancreatography diagnosed PPF in 8 (80 %) of 10 patients. Twenty-one patients (65 %) improved with conservative management alone. Interventional therapy (5 endoscopic and 6 surgical interventions) was eventually needed in 35 percent of the patients after failing conservative management. Magnetic resonance cholangiopancreatography is the better initial choice for being a noninvasive procedure and for better demonstration of complete main pancreatic duct obstruction. Restoring anatomic continuity is important if conservative approach fails [286].

Maldigestion and nutrition

Vitamins

The main clinical manifestations of exocrine pancreatic insufficiency are fat malabsorption, known as steatorrhea, which consists of fecal excretion of more than 6 g of fat per day, weight loss, abdominal discomfort and abdominal swelling sensation. Fat malabsorption also results in a deficit of fat-soluble vitamins (A, D, E and K) with consequent clinical manifestations. The relationships between pancreatic maldigestion, intestinal ecology and intestinal inflammation have not received particular attention, even if in clinical practice these mechanisms may be responsible for the low efficacy of pancreatic extracts in abolishing steatorrhea in some patients. The best treatments for pancreatic maldigestion should be re-evaluated, taking into account not only the correction of pancreatic insufficiency using pancreatic extracts and the best duodenal pH to permit optimal efficacy of these extracts, but we also need to consider other therapeutic approaches including the decontamination of intestinal lumen, supplementation of bile acids and, probably, the use of probiotics which may attenuate intestinal inflammation in chronic pancreatitis patients [287].

Nutritional support

Chronic pancreatitis is associated with a substantial morbidity, including malnutrition, malabsorption, pseudocysts, metabolic disturbances, and intractable abdominal pain. Approximately 5 percent of patients with chronic pancreatitis are refractory to nutritional support and opiate analgesia, making management challenging. Pancreatic rest can provide symptomatic relief. However, achieving simultaneous pancreatic rest and adequate nutritional support in these patients is difficult. It was describe a technique for providing nutritional support and pancreatic rest in patients with intractable symptomatic in 3 patients. All 3 patients had masses associated with the pancreas. Symptom relief and adequate nutritional support were achieved by inserting a long-term nasojejunal tube (Flocare Bengmark, Nutricia Clinical Care, United Kingdom) under ambulatory endoscopic guidance. The long-term nasojejunal tube feeding achieved pancreatic rest and significant symptomatic relief while delivering adequate nutritional support. Pseudocyst size decreased substantially in 2 patients. The third patient was found to have pancreatic carcinoma after pancreaticoduodenectomy [288].

Influence of colostrums

Exocrine pancreatic secretion contributes to limit pathogenic bacteria-associated diarrhea. Bovine colostrum, used in the treatment of diarrhea, reduces symptoms originating from gut pathogenic bacteria overgrowth. It was hypothesized that bovine colostrum may stimulate the exocrine pancreatic secretion. Eighteen piglets fitted with 2 permanent catheters (for pancreatic juice collection and reintroduction) were allocated to 1 of the following 2 dietary treatments for 5 days: a control diet or a diet supplemented with defatted bovine colostrum. Pancreatic juice was collected daily, and digestive enzyme activities and antibacterial activity were determined. The prandial pancreatic juice outflow, the basal and prandial lipase output, and the basal secretion of the antibacterial activity were, respectively, 60 percent, 154 percent, 92 percent, and 72 percent higher in piglets fed a diet supplemented with defatted bovine colostrum. It was concluded that with defatted bovine colostrum, the increased antibacterial activity secretion against Escherichia coli may limit pathogenic bacteria overgrowth of the gut and reduce diarrheal episodes. The role of secretin in the increased pancreatic juice flow and lipase secretion was considered [289].

Diabetes in chronic pancreatitis

In consequence of the close anatomical and functional links between the exocrine and endocrine pancreas, any disease affecting one of these parts will inevitably affect the other. Pancreatic conditions which might cause diabetes mellitus include acute and chronic pancreatitis, pancreatic surgery, cystic fibrosis and pancreatic cancer. The development of diabetes greatly influences the prognosis and quality of life of patients with exocrine pancreatic diseases. It may cause lifethreatening complications, such as hypoglycemia, due to the lack of glucagon and the impaired absorption of nutrients, or the micro- and macrovascular complications may impair the organ functions. Temporary hyperglycemia can be observed in around 50 percent of patients with acute pancreatitis; persisting diabetes mellitus may affect 1-15 percent. The prevalence of diabetes in chronic pancreatitis varies between 30 and 83 percent. Overall, exocrine pancreatic diseases are believed to be responsible for diabetes in only about 0.5-1.7 percent of the cases, but in as many as 15-20 percent of diabetes mellitus patients in Southeast Asia, where tropical pancreatitis is endemic. The incidence of pancreatic diabetes depends on several factors, such as the etiology and duration of chronic pancreatitis, and the presence of pancreatic calcification. The endocrine function is more disturbed in alcoholic chronic pancreatitis than in nonalcoholic pancreatitis. Both insulin and glucagon secretion are more strongly impaired in patients with calcified chronic pancreatitis than in those with noncalcified chronic pancreatitis. In two recent follow-up studies of patients with chronic pancreatitis over a period of 7.7 and 8

years, the risk of diabetes was increased 3.2- and 1.3-fold, respectively, after the onset of pancreatic calcification. Clinically manifest diabetes usually appears in the advanced stages of the disease, generally 8-10 years after the onset. The longer the duration of pancreatitis, the higher the number of patients who develop diabetes. The annual rate of diabetes in chronic pancreatitis calculated by means of linear regression was 3.5 percent and the cumulative rate of diabetes 25 years after the onset of chronic pancreatitis was 83 percent. Distal pancreatectomy was associated with a higher rate of diabetes as compared with other types of surgical procedures (pancreaticoduodenectomy, or pancreatic drainage) or with patients who were never treated surgically. This result is consistent with the distribution of Langerhans' islets in the pancreatic gland: the islet concentration of the tail is significantly greater than the concentration in the head and body. There is a regional distribution of the glucagon-producing delta-cell and pancreatic polypeptide (PP)-producing cell, based on the embryologic derivation of the pancreas from distinct dorsal and ventral anlagen. The dorsal pancreas contains the glucagon-rich islets, whereas the ventral pancreas (most of the head and the uncinate process) is PP-rich. The role of PP deficiency in the pathogenesis of pancreatic diabetes suggests that conservation of the PP-rich ventral pancreas may be important for improved outcome after surgical treatment of pancreatic disease. Around 70 percent of patients with pancreatic cancer already have an impaired glucose tolerance or frank diabetes. In nearly 60 percent of these, the impaired glucose tolerance or diabetes improves after surgery, whereas diabetes does not develop during a short-term follow-up. The reasons for the impaired glucose metabolism in pancreatic cancer are the alterations caused in the islet cell functions by diabetogenic substances released by the cancer cells. On the other hand, 30 percent of the patients with a benign form of the disease and normal preoperative glucose tolerance become diabetic after surgery. The primary hormonal abnormality in pancreatic diabetes is decreased insulin secretion. In chronic pancreatitis, the progressive fibrosis destroys the beta-cells and reduces their functional capacity, leading to a deficiency of insulin secretion. Furthermore, the fibrosis impairs the circulation in the islets, which may result in an impaired delivery of secretagogues and blunted hormonal responses of the islets. Moreover, pancreatic diabetes is considered to be a result not merely of an impaired insulin production, but also of coexisting insulin resistance and alterations in insulin action. The loss of hepatic insulin receptor expression caused by PP deficiency and impairment of combined insulin receptor and glucagonlike peptide 2 endocytosis after insulin binding in chronic pancreatitis was recently demonstrated to contribute to the development of diabetes. The greater the reduction in beta-cell mass, the more the insulin secretion is impaired and the more the glucose tolerance is reduced. As long as 20-40 percent of the beta-cell mass is preserved, the fasting plasma glucose and insulin levels are often normal. Nevertheless, at this stage, the functional exhaustion of the endocrine pancreas may be revealed by stimulatory tests: the insulin responses following the ingestion of an oral glucose load or arginine or glucagon infusion are already delayed and reduced. Only when around 80 percent of the beta-cells have been destroyed does fasting hyperglycemia develop. However, pancreatic diabetes has distinct clinical characteristics: the wide fluctuations in plasma glucose and frequent, severe and unpredictable hypoglycemic episodes which may be lethal. This is particularly true for patients with pancreatic diabetes caused by total or subtotal pancreatectomy due to:

- basal glucagon secretion is significantly lower in those with pancreatic diabetes as compared with patients with primary diabetes or healthy controls due to the reduction in beta-cell mass. The hypoglycemia and the arginine-stimulated glucagon response are lower in pancreatic diabetes. The effects of insulin therefore remain unopposed due to impaired glucagon secretion
- the maldigestion of carbohydrates due to the coexisting pancreatic exocrine insufficiency
- concomitant alcohol consumption and hepatic disease
- the lack of compliance with the prescribed diet and medical therapy
- enhanced intestinal transit

Unlike hypoglycemia, the development of diabetic ketoacidosis and coma are uncommon in pancreatic diabetes, and are mainly seen in situations of marked stress such as infections or surgery. This can be explained by the fact that the secretion of insulin is markedly impaired in pancreatic diabetes, but, except for total pancreatectomy, never completely absent. The development of early microvascular complications in pancreatic diabetes is similar to that in other forms of diabetes. The prevalence and severity of diabetic retinopathy and neuropathy in pancreatic diabetes patients do not differ from those in patients with insulin-dependent diabetes, and depend on the duration of the diabetes and on the degree of adequacy of glycemic control. The prevalence of more advanced stages of diabetic microvascular complications is not well known because of the high mortality of patients with chronic pancreatitis. The prevalence of neuropathy may be observed in 30 percent of the patients with pancreatic diabetes, but an early onset suggests that the peripheral nerves had already been damaged by longterm alcohol abuse. The prevalence of diabetes in patients with autoimmune pancreatitis is quite high as compared with that in patients with ordinary chronic pancreatitis and is diagnosed before or simultaneously with autoimmune pancreatitis in 85 percent of the patients. Steroid therapy reduces the symptoms of diabetes in approximately 50 percent of patients with autoimmune pancreatitis. Diabetes is caused by cytokines from T-cells and macrophages, which suppress the function of the islet beta-cells. This suppression may be downregulated by steroids. On the other hand, 14 percent of the patients, and particularly older patients, exhibit newly developed diabetes or exacerbation of diabetes after steroid therapy as steroids counteract the effects of insulin. The treatment of pancreatic diabetes, a distinct metabolic and clinical form of diabetes, requires special knowledge. Diet and pancreatic enzyme replacement therapy may be sufficient in the early stages. Oral antidiabetic drugs are not recommended. If the diet proves inadequate to reach the glycemic goals, insulin treatment with multiple injections is required. The goal of treatment in pancreatic diabetes is therefore to achieve a HbA 1C level as close as possible to normal in the absence of hypoglycemia. However, this goal may be difficult to achieve with the present therapies. The irregular lifestyle of patients with pancreatic diabetes, their random eating habits, the lack of compliance, maldigestion and alcohol consumption severely hamper their treatment. Alcohol abstinence and appropriate enzyme substitution are essential to reduce the metabolic instability. The absorption of nutriments is unpredictable without adequate enzyme replacement therapy; the glucose-lowering effect of insulin occurs earlier than the glucose-elevating effect of nutriments, thereby leading to hypoglycemia. The basic principles of nutrition therapy are the same as those applied in other forms of diabetes: the daily carbohydrate and energy intake should be based on the body weight and physical activity and meals should be rich in vegetable fibers and low in fat. Eating frequent small-volume meals, at least six times per day, is recommended in pancreatic diabetes. The intake of saturated fatty acids from animal sources must be reduced, but decreasing the use of vegetable oil is also suggested. Milk and dairy products with reduced fat contents are recommended. The intake of gross fibers is not advised as they may cause gastrointestinal symptoms due to the exocrine pancreatic insufficiency. The application of oral antidiabetic drugs in pancreatic diabetes is not recommended. Insulin sensitizers (biguanides and glitazones) and the carbohydrate absorption inhibitor glucosidase inhibitors should be avoided in pancreatic diabetes since the major pathogenetic defect is the lack of insulin and because of the coexisting maldigestion and consequent leanness. Although patients with pancreatic diabetes may occasionally be capable of insulin secretion, the use of sulfonylureas is likewise not recommended, because they can accelerate the exhaustion of beta-cells. Furthermore, they are often contraindicated due to the accompanying liver disease. Appropriate glycemic control can be achieved in pancreatic diabetes by the administration of short-acting insulin three times per day and an intermediate insulin injection before sleep. The dosage of this bedtime insulin is usually much less than that in type 1 diabetes. The administration of long-acting insulin twice a day is not recommended in pancreatic diabetes, because of the possibility of interference and the danger of severe hypoglycemia. Treatment with oral pancreatic enzymes is therefore indicated in diabetes

patients with a proven exocrine pancreatic insufficiency [290].

Function in diabetes mellitus

Recently it has been shown that there is not only endocrine insufficiency in diabetic patients, but a frequent co-morbidity of both, the endocrine and exocrine pancreas. The records of 1992 patients with diabetes mellitus who had been treated in one hospital during a 2-year period were re-evaluated. Defined parameters were documented in standardized data sheets. Records were further checked for the results of imaging procedures of the pancreas. In 307 patients fecal elastase-1 concentrations had been performed and documented. Only these patients were included in further evaluation. Fecal elastase-1 concentrations were inversely correlated with diabetes duration and HbA1c-levels but not with age. C-peptide levels correlated positively with fecal elastase-1 concentrations. BMI and fecal elastase-1 concentrations were also significantly correlated. There was no correlation between diabetes therapy and exocrine pancreatic function as there was no correlation with any concomitant medication. The presence of diabetes-associated antibodies was not related to fecal elastase-1 concentrations. According to the documented data 38 were classified as type-1 diabetes (12 %), 167 as type-2 (54 %), and 88 patients met the diagnostic criteria of type-3 (29 %). Fourteen patients could not be classified because of lacking information (5 %). The authors concluded that exocrine insufficiency might be explained as a complication of diabetes mellitus. However, it is more likely that type-3 diabetes is much more frequent than previously believed. Consequently the evaluation of exocrine function and morphology should be included into the clinical workup of any diabetic patient at least at the time of manifestation [291].

Pancreas divisum

To assess the long-term outcomes of endoscopic minor papilla therapy in a spectrum of symptomatic patients with pancreas divisum. Patients with pancreas divisum coded in a prospective database as having had minor papilla endotherapy (1997- 2003, n=145) were grouped into 3 categories: (1) acute recurrent pancreatitis, (2) chronic pancreatitis, and (3) chronic/recurrent epigastric pain. Telephone follow-up was conducted (78 % of patients), including quesions regarding interval co-interventions and narcotic use. Primary success was defined as clinical improvement (better or cured on a Likert scale), without needing narcotics, after one therapeutic endoscopic retrograde cholangiopancreatography. Primary success rates in acute recurrent pancreatitis, chronic pancreatitis, and chronic/recurrent epigastric pain were achieved in 53 percentage, 18 percent, and 41 percent, respectively; and secondary success rates ($\leq$ 2 additional endoscopic retrograde cholangiopancreatographies), 71 percent, 46 percent, and 55 percent, respectively (median follow-up, 43 months; range, 14-116 months). Younger age (median age, 47 years [no success] vs 58 years [success]) and chronic pancreatitis (odds ratio, 0.10; 95 % confidence interval 0.03 to 0.39) independently predicted a lower chance of success. It was concluded that significant long-term improvement can be achieved with endoscopic therapy in selected patients with pancreas divisum, although many require multiple procedures. Older patients, without chronic pancreatitis, were most likely to respond [292].

Pancreatic stellate cells

Pancreatitis and pancreatic cancer represent two major diseases of the exocrine pancreas. Pancreatitis exhibits both acute and chronic manifestations. The commonest causes of acute pancreatitis are gallstones and alcohol abuse; the latter is also the predominant cause of chronic pancreatitis. Recent evidence indicates that endotoxinemia, which occurs in

alcoholics due to increased gut permeability, may trigger overt necroinflammation of the pancreas in alcoholics and one that may also play a critical role in progression to chronic pancreatitis (acinar atrophy and fibrosis) via activation of pancreatic stellate cells (PSCs). Chronic pancreatitis is a major risk factor for the development of pancreatic cancer, which is the fourth leading cause of cancer-related deaths in humans. Increasing attention has been paid in recent years to the role of the stroma in pancreatic cancer progression. It is now well established that PSCs play a key role in the production of cancer stroma and that they interact closely with cancer cells to create a tumor facilitatory environment that stimulates local tumor growth and distant metastasis. One review summarized recent advances in the understanding of the pathogenesis of alcoholic pancreatitis and pancreatic cancer, with particular reference to the central role played by PSCs in both diseases. An improved knowledge of PSC biology has the potential to provide an insight into pathways that may be therapeutically targeted to inhibit PSC activation, thereby inhibiting the development of fibrosis in chronic pancreatitis and interrupting stellate cell-cancer cell interactions so as to retard cancer progression [293].

Pancreatic duct stones

Although radiopaque pancreatic duct stones can be targeted by extracorporeal shock wave lithotripsy (ESWL) and extracted by ERCP, large and radiolucent stones remain a therapeutic challenge. Four symptomatic patients with large ($\geq$ 1 cm) radiolucent stones occluding the main pancreatic duct that could not be retrieved by standard endoscopic maneuvers. Pancreatic sphincterotomy followed by balloon dilation of the pancreatic orifice to aid retrieval of large radiolucent stones occluding the main pancreatic duct was performed. Technical success was defined as the ability to achieve pancreatic duct clearance in one endoscopic encounter. The procedure was technically successful in all 4 patients. Pancreatic duct clearance was achieved in all 4 patients in 1 endoscopy session with complete symptom relief at 12-month follow-up. Mild post-ERCP pancreatitis developed in 1 patient, and minor bleeding developed in another patient; both were managed conservatively. It was concluded that endoscopic balloon dilation of the pancreatic orifice after sphincterotomy is a safe technique that facilitates the removal of large radiolucent stones from the main pancreatic duct in [294].

Duodenal dystrophy

One paper presented the morphological characteristics of intraoperative specimens taken from patients with duodenal dystrophy characterized by cystic changes in the elements of pancreatic heterotopic tissue in the duodenal wall. It is emphasized that the development of cysts may be associated with that of an inflammatory process in the pancreatic heterotopic tissue in young persons or may be caused by chronic alcoholic pancreatitis [295].

On the basis of a review of the literature and description of a clinical case, the aim of one paper was to evaluate the role of pancreaticoduodenectomy as the primary therapeutic choice in a rare, serious condition such as cystic dystrophy of the duodenal wall in heterotopic pancreas. The diagnosis is difficult because of the non-specific clinical manifestations, and radiological and endoscopic imaging are decisive. Computed tomography and magnetic resonance are very useful for demonstrating the presence of cysts in a thickened duodenal wall but endoscopic ultrasonography is the most useful imaging examination. The choice of therapeutic option is still debated. Although some authors have proposed a medical approach using octreotide or endoscopic treatment for selected patients, pancreaticoduodenectomy is usually proposed for symptomatic patients. When surgery is needed, pancreaticoduodenectomy should be preferred, reserving by-pass procedures for

high-risk patients [296].

Cystic fibrosis

Cystic fibrosis is an autosomal recessive disorder, which is caused by a mutation in the CFTR protein, a chloride channel in epithelial cell membranes. More than 1500 mutations are known. The incidence is 1/2.000-3.000 in nations of European origin. The CFTR mutation influences the secretion and absorption by epithelium in various organs. The consequences are different depending on the organ, but there is a global tendency for obstruction of secretory glands. The primary organs affected are the respiratory tract, pancreas, gastrointestinal tract and sweat glands. The disease is most often diagnosed during the first months of life, with a common presentation of salty tasting sweat, failure to thrive and diverse faecal problems. Possible diagnostic tools are sweat test and DNA testing. Respiratory symptoms cause most morbidity, with chronic infections and an exaggerated inflammatory response. Abnormal water and electrolyte composition leads to thicker respiratory secretions compared to that of healthy individuals. The interaction of pathogens with the epithelium causes S. aureus, and later P. aeuruginosa, to transform into a mucoid form which is much more difficult to eradicate with antibiotics, making them a significant part of the disease burden of cystic fibrosis. The main respiratory medications are antibiotics, bronchodilators, mucolytic agents and anti-inflammatory agents. Ninty percent of cystic fibrosis patients have pancreas insufficiency which is treated with pancreas enzymes. A good nutritional status is a necessary basis for any further treatment. The prognosis of cystic fibrosis patients has improved greatly over the last few decades in parallel with increased knowledge, and the average survival is currently 37 years in the United States [297].

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis is a systemic disease with a wide range of pancreatic and extrapancreatic imaging findings. These findings can mimic those of other diseases in the pancreas or other organs and therefore are commonly misdiagnosed and mistreated. It is important for radiologists to understand both the pancreatic and extrapancreatic imaging findings of autoimmune pancreatitis to make accurate and timely diagnoses [298].

Pathogenesis

Tumor growth factor-beta (TGF-beta) is an immunosuppressive cytokine and has been implicated in a variety of disease processes, including those in autoimmune disease. Tumor growth factor-beta is also involved in fibrosis by regulating matrix metalloproteinases (MMPs) and the tissue inhibitor of MP (TIMP). The purpose of one study was to compare the expression patterns of TGF-beta1, MMP-2, and TIMP-2 between autoimmune chronic pancreatitis (AIP) and alcoholic chronic pancreatitis (ACP) by immunohistochemical staining of pancreatic tissue specimens. Pancreatic tissue specimens were obtained from 16 of 57 patients who had a diagnosis of AIP. Pancreatic tissue specimens of ACP were obtained from 10 patients who were surgically treated. The degree of immunohistochemical staining for TGF-beta1 was significantly weaker in AIP than in ACP in the pancreatic ductal epithelial and mononuclear cells. This finding suggests that there may be a defect in the function of regulatory T (Treg) cells, which normally prevents autoimmune disease progression via a suppressor mechanism. Further studies are needed to identify the type of regulatory T cell involved in this process [299].

Inflammatory pseudotumor (IPT) is a heterogeneous group of lesions occurring in various organs, which is histologically characterized by fibroblastic and myofibroblastic proliferation with inflammatory infiltrate. Inflammatory myofibroblastic tumor (IMT) is a neoplastic counterpart of IPT, which shows aberrant expression of ALK and its gene translocation. In contrast, the concept "immunoglobulin (Ig)G4-related IPT" in the lung, liver, and pancreas has recently been proposed as a member of IgG4-related sclerosing disease. In one study, it was compared the histopathologic features with an emphasis on IgG4 expression between 22 cases of IMT and 16 cases of IgG4-related sclerosing disease, including chronic sclerosing sialadenitis (n=8), mass-forming autoimmune pancreatitis (n=3), sclerosing cholangitis (n=1), retroperitoneal fibrosis (n=2), and chronic sclerosing dacryoadenitis (n=2). Bland-looking spindle cell proliferation with fibrosis and inflammatory infiltrate of lymphocytes and plasma cells was the common morphologic feature in both lesions. Obstructive phlebitis was observed in all of the IgG4-related sclerosing lesions, but in only 1/22 of IMT. The immunohistochemical expression of ALK was observed in 15/22 (68 %) of IMT and 0/16 (0 %) of IgG4-related sclerosing disease. The number of IgG4-positive plasma cells and the ratio of IgG4+/ IgG+ plasma cells were each significantly lower in IMT than in IgG4-related sclerosing disease. The results suggest that IgG4 does not play an important role in the pathogenesis of IMT. In addition, the evaluation of IgG4+ plasma cells and the ratio of IgG4+/IgG+ plasma cells and the presence of obstructive phlebitis may be useful for the differential diagnosis between IMT and IgG4-related sclerosing disease [300].

Association with Helicobacter pylori

It was studied the frequency of peptic ulcer, the association of peptic ulcer with Helicobacter pylori and host TNF-alpha promoter haplotype in autoimmune pancreatitis (AIP) and nonautoimmune chronic pancreatitis. Esophagogastroduodenoscopy (EGD) was performed in 40 patients with AIP and 113 patients with nonautoimmune chronic pancreatitis. The status of H. pylori infection was determined. Genotyping and 5-locus haplotype assembly of the

TNF-alpha promoter were performed. The correlation between clinical characteristics, endoscopic findings, Helicobacter pylori infection status, and TNF-alpha promoter polymorphism and haplotype was analyzed. The frequencies of gastric ulcer (GU) were significantly higher in patients with autoimmune pancreatitis compared with patients with nonautoimmune CP (23 % vs 4 %). Duodenal ulcer (DU) was more prevalent than GU in both patients with AIP and patients with nonautoimmune chronic pancreatitis. There was no difference in the positive status of Helicobacter pylori and TNF-alpha promoter polymorphism/haplotype. The results demonstrated that gastric ulcer was more prevalent in AIP compared with nonautoimmune chronic pancreatitis. Positive H. pylori status and host TNF-alpha promoter susceptibility could not explain the pathogenesis of higher gastric ulcer prevalence and pathogenesis of autoimmune pancreatitis in a selected population [301].

Association with eosinophilia

The purpose of one study was to investigate the clinical significance and causes of eosinophilia (>0.5 x 10^9/L eosinophils in the peripheral blood) by analyzing the features of chronic pancreatitis cases with eosinophilia. It was retrospectively analyzed the clinical features of chronic pancreatitis patients with eosinophilia and compared them with chronic pancreatitis patients without eosinophilia. There were 28 cases (16 %) with eosinophilia among 180 patients with chronic pancreatitis. The peak value of eosinophils in the patients' peripheral blood was 0.935 $\pm$ 0.600 x 10^9/L. The incidence of eosinophilia in autoimmune pancreatitis was significantly higher than in non-autoimmune pancreatitis chronic pancreatitis cases. The incidence of pancreatic ascites, pancreatic enlargement, or jaundice in with eosinophilia was significantly higher than in those without eosinophilia. There was no obvious infiltration of eosinophils in the pancreatic tissues of 16 pathology or cytology specimens. It was concluded that the occurrence of eosinophilia during the course of chronic pancreatitis is not unusual. This may be related to autoimmune mechanisms, serous membrane response, or the progression of pancreatic inflammation and fibrosis [302].

Definitions and differential diagnosis

Three committees (the professional committee for making clinical questions and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators) were organized. Fifteen specialists for Japanese clinical guidelines for autoimmune pancreatitis extracted the specific clinical statements from a total of 871 literatures by PubMed search (~1963-2008) and from a secondary database and made the clinical questions and statements. The expert panelists individually rated these clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than 7 on a 9-point scale from the panel was regarded as valid. The professional committee made 13, 6, 6, and 11 clinical questions and statements for the concept and diagnosis, extrapancreatic lesions, differential diagnosis, and treatment, respectively. The expert panelists regarded them as valid after a 2-round modified Delphi approach. After evaluation by the moderators, the Japanese clinical guideline for AIP has been established [303].

The new Japanese clinical guidelines for autoimmune pancreatitis (JCGAIP) reflect a careful, consensus-building effort to guide and standardize the diagnosis and treatment of patients with autoimmune pancreatitis in Japan. The guidelines provide an effective review of autoimmune pancreatitis and merit attention and careful consideration regarding their application internationally. The most basic issue is the question of whether there is more than one form of autoimmune pancreatitis in regard to pancreatic pathology, clinical features, and pathogenetic mechanisms. The JCGAIP focus on patients with the histopathologic changes called lymphoplasmacytic sclerosing pancreatitis (LPSP), most of whom have elevations of plasma immunoglobulins, and specifically of IgG4. It has been proposed that AIP is a

manifestation of a systemic IgG4-related autoimmune disease. These patients are typically older than 50 years and male. Large series reported from Europe and the United States consistently identify a second set of patients with slightly different histopathologic changes that have been called idiopathic duct-centric chronic pancreatitis (IDCP) or AIP with granulocytic epithelial lesions (GELs). This subgroup of patients is more diverse in age, includes a higher fraction of female patients, and characteristically does not have elevated plasma IgG4. These patients may have chronic inflammatory bowel disease such as ulcerative colitis, but typically lack evidence of extrapancreatic involvement of the organs typical of IgG4-related autoimmune disease. More recently, these two patterns have been designated as AIP types 1 and 2. In the United States and Europe, type 1 AIP (LPSP) is more common than type 2 (IDCP/AIP with GELs) in series that identify both types. Both types of AIP share a number of histopathologic features most notably a periductal lymphoplasmacytic infiltrate and a phlebitis. Only the concomitant duct infiltration by neutrophilic granulocytes, the GEL, and a less marked phlebitis distinguish the histological changes of type 2 from type 1 AIP. A fraction of patients with type 2 AIP also has inflammatory bowel disease, and one had multiple sclerosis (some forms of multiple sclerosis are considered to be of autoimmune origin). Type 2 AIP patients may also show biliary involvement similar to that seen in type 1 AIP. Finally, both types 1 and 2 AIP cases reveal a similar increase in the numbers of CD4 and CD lymphocytes that infiltrate the pancreas. In aggregate, these observations provide a significant support for an autoimmune mechanism in the pathogenesis of type 2 AIP. The issue of core biopsies to diagnose AIP has been a point of contention. Whereas the Mayo group has published on the technical aspects and usefulness of endoscopic ultrasoundguided pancreatic core biopsies and routinely uses it to establish the diagnosis of AIP, others have not found it as helpful in its ability to get sufficient tissue to make the diagnosis of either AIP or nonfocal chronic pancreatitis. The American criteria also differ sigificantly from the Japanese and Asian criteria in the use of serological markers. Whereas the American criteria use only serum IgG4, the Japanese and Asian criteria use any one of immunoglobulin G, immunoglobulin G4, and autoantibodies such as antinuclear antibody and rheumatoid factor. However, unlike the American criteria, in the Japanese or Asian criteria, other organ involvement cannot be used as collateral evidence to diagnose AIP.It is believe that the presence of other organ involvement can be as helpful as, if not more helpful than, serological abnormalities in the diagnosis of AIP and should be included in the diagnostic armamentarium as suggested by the JCGAIP. In conclusion, the new Japanese guidelines reflect progress in standardizing the diagnosis and treatment AIP. The recommendations also reveal differences in the experience of Japanese and Western clinicians and pathologists that may require additional consideration for their application internationally, or slight revision to create guidelines that are applicable worldwide [304].

A new antibody

Autoimmune pancreatitis is characterized by an inflammatory process that leads to organ dysfunction. The cause of the disease is unknown. Its autoimmune origin has been suggested but never proved, and little is known about the pathogenesis of this condition. To identify pathogenetically relevant autoantigen targets, it was screened a random peptide library with pooled IgG obtained from 20 patients with autoimmune pancreatitis. Peptide-specific antibodies were detected in serum specimens obtained from the patients. Among the detected peptides, peptide AIP(1-7) was recognized by the serum specimens from 18 of 20 patients with autoimmune pancreatitis and by serum specimens from 4 of 40 patients with pancreatic cancer, but not by serum specimens from healthy controls. The peptide showed homology with an amino acid sequence of plasminogen-binding protein (PBP) of Helicobacter pylori and with ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), an enzyme highly expressed in acinar cells of the pancreas. Antibodies against the PBP peptide were detected in 19 of 20 patients with autoimmune pancreatitis (95 %) and in 4 of 40 patients with pancreatic cancer (10 %). Such reactivity was not detected in patients with alcohol-induced chronic pancreatitis or intraductal papillary mucinous neoplasm. The results

were validated in another series of patients with autoimmune pancreatitis or pancreatic cancer: 14 of 15 patients with autoimmune pancreatitis (93 %) and 1 of 70 patients with pancreatic cancer (1 %) had a positive test for anti-PBP peptide antibodies. When the training and validation groups were combined, the test was positive in 33 of 35 patients with autoimmune pancreatitis (94 %) and in 5 of 110 patients with pancreatic cancer (5 %). It was concluded that the antibody that was identified was detected in most patients with autoimmune pancreatitis but also in a few patients with pancreatic cancer, making it an imperfect test to distinguish between these two conditions [305].

Possible etiological factors

K-ras

To assess the relationship between autoimmune pancreatitis (AIP) and pancreatic cancer, it was analyzed K-ras mutation in the pancreatobiliary tissues of patients with AIP. An analysis of K-ras mutation and an immunohistochemical study were performed on the pancreas of 8 patients with autoimmune pancreatitis and 10 patients with chronic alcoholic pancreatitis and on the common bile duct and the gallbladder of 9 patients with AIP. K-ras mutation was analyzed in the pure pancreatic juice from 3 patients with AIP. High-frequency K-ras mutation (2+ or 3+) was detected in the pancreas of all the 8 patients and in the pancreatic juice of the other 2 patients. The mutation in codon 12 of the ras gene was GAT in all the 10 patients. High-frequency K-ras mutation was detected in the common bile duct of 5 patients with autoimmune pancreatitis and in the gallbladder epithelium of 4 patients with AIP. The K-ras mutation was detected in the fibroinflammatory pancreas, the bile duct, and the gallbladder, with abundant infiltrating IgG4-positive plasma and Foxp3-positive cells of patients with AIP with elevated serum IgG4 levels. It was concluded that significant K-ras mutation occurs most frequently in the pancreatobiliary regions of patients with AIP. Autoimmune pancreatitis may be a risk factor of pancreatobiliary cancer [306].

TGF-beta1

Tumor growth factor-beta (TGF-beta) is an immunosuppressive cytokine and has been implicated in a variety of disease processes, including those in autoimmune disease. Tumor growth factor [beta] is also involved in fibrosis by regulating matrix metalloproteinases (MMPs) and the tissue inhibitor of MP (TIMP). The purpose of one study was to compare the expression patterns of TGF-beta1, MMP-2, and TIMP-2 between autoimmune chronic pancreatitis (AIP) and alcoholic chronic pancreatitis (ACP) by immunohistochemical staining of pancreatic tissue specimens. Pancreatic tissue specimens were obtained from 16 of 57 patients who had a diagnosis of AIP. Pancreatic tissue specimens of alcoholic chronic pancreatitis were obtained from 10 patients who were surgically treated. The degree of immunohistochemical staining for TGF-beta1 was significantly weaker in AIP than in alcoholic chronic pancreatitis in the pancreatic ductal epithelial and mononuclear cells. This finding suggests that there may be a defect in the function of regulatory T (Treg) cells, which normally prevents autoimmune disease progression via a suppressor mechanism. Further studies are needed to identify the type of regulatory T cell involved in this process [307].

Extrapancreatic manifestations

The frequency and clinical characteristics of extrapancreatic lesions during the clinical course of autoimmune pancreatitis were investigated retrospectively in 64 patients with autoimmune pancreatitis. The predictive factors for relapse of autoimmune pancreatitis at clinical onset

were also examined. Extrapancreatic lesions occurred in 95 percent (61/64) during the clinical course of autoimmune 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. It was thus concluded that the frequency of extrapancreatic lesions with autoimmune pancreatitis during the clinical course was high. The presence of sclerosing sialadenitis at clinical onset is a significant predictive factor for relapse of autoimmune pancreatitis [308].

Mikulicz disease

Patients with autoimmune pancreatitis sometimes present with Mikulicz disease; however, the clinical features regarding these autoimmune pancreatitis patients with Mikulicz disease have not yet been fully elucidated. The aim of one study was to study the clinical differences between autoimmune pancreatitis with and without Mikulicz disease. Twenty-eight autoimmune pancreatitis patients were divided into 2 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: gender; 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 autoimmune pancreatitis and 23 autoimmune pancreatitis patients, respectively. The results of univariate analysis revealed that autoimmune pancreatitis patients presenting with Mikulicz disease were significantly associated with a younger onset, female predominance, high serum IgG4 titer, and diffuse pancreatic swelling. In 4 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 [309].

Sclerosing cholangitis

It was assessed the clinical, computed tomography, and pathological findings in patients with lymphoplasmacytic sclerosing cholangitis in 15 consecutive patients (four women and 11 men, mean age 71 years) with lymphoplasmacytic sclerosing cholangitis and without the characteristic features of underlying disorders causing benign biliary strictures were retrospectively recruited. Two radiologists evaluated multiphase contrast-enhanced CT images acquired with 0.5 or 1-mm collimation. One pathologist performed all histological examinations, including IgG4 immunostaining. The intrahepatic biliary ducts showed dilatation in all 15 patients, but only seven presented with jaundice. Although laboratory data were not available in all patients, serum gammaglobulin and IgG levels were elevated in five of six patients and six of eight patients, respectively. Anti-nuclear antibody was detected in three of six patients. The involved biliary ducts showed the following CT findings: involvement of the hilar biliary duct (14/15), a mean wall thickness of 4.9 mm, a smooth margin (10/15), a narrow but visible lumen (6/15), hyper-attenuation during the late arterial phase (9/15), homogeneous hyper-attenuation during the delayed phase (11/11), and no

vascular invasion (14/15). Abnormal findings in the pancreas and urinary tract were detected in eight of 15 patients. In 13 patients with adequate specimens, moderate to severe lymphoplasmacytic infiltration associated with dense fibrosis was observed. Infiltration of IgG4-positive plasma cells was moderate or severe in nine patients and minimal or absent in four patients. It was concluded that lymphoplasmacytic sclerosing cholangitis exhibits relatively characteristic clinical and CT findings, although they are not sufficiently specific for differentiation from other biliary diseases [310].

Retroperitoneal fibrosis

It was presented a case of retroperitoneal fibrosis (RPF) in a 72-year-old man who previously received pancreatectomy for autoimmune pancreatitis. He had earlier received colectomy for early colon cancer. During the routine follow-up for colon cancer, a swollen pancreas tail was detected on enhanced CT. He received distal pancreatectomy under the diagnosis of pancreas cancer two years later. Pathological diagnosis revealed the autoimmune pancreatitis. Eight months later, right hydronephrosis was observed in an abdominal ultrasonographic study, and at the same time, right hydroureterosis due to retroperitoneal soft tissue mass around the bifurcation was detected on enhanced CT. He was treated with predonisolone aiming at the diagnosis and therapy. Twelve weeks later, right hydronephrosis had disappeared and retroperitoneal mass had shrunken. Now, it is thought that autoimmune pancreatitis is a systemic sclerosing disease accompanied with extra-pancreatic pathologic changes such as RPF [311].

A 74-year-old male patient presented with progressive anorexia, cholestatic liver function tests, and a diffuse enlarged pancreas suggestive of a pancreatic carcinoma. There was a marked elevation of total immunoglobulin G4 (IgG4) in serum. Further investigation led to the diagnosis of IgG4-related sclerosing disease with involvement of the pancreas, retroperitoneal fibrosis, and bilateral focal nephritis. This was the first report on these three clinical entities occurring in the same patient. A short review of the literature concerning autoimmune pancreatitis and retroperitoneal fibrosis is made, with special interest to the concept of IgG4-related pathology. This systemic disease can have several clinical manifestations: IgG4-positivity not only can be found in the pancreas, but also at the level of extrahepatic biliary ducts, gallbladder, salivary glands, retroperitoneal tissue, kidneys, ureters, and lymph nodes [312].

Diagnostics

CT

It was investigated the clinical and radiological features of focal mass-forming autoimmune pancreatitis (FMF AIP) to help physicians avoid performing unnecessary surgery because of an improper diagnosis. It was evaluated 23 patients with chronic inflammatory pancreatic masses and who underwent pancreatectomy for presumed pancreatic cancer from 1995 to 2005. These patients were distinguished into 8 FMF AIP patients and 15 ordinary chronic pancreatitis patients through a histological review, along with considering the immunoglobulin G4 staining. Twenty-six randomly selected pancreatic cancer patients were also evaluated as a control group. On the portal venous phase of computed tomography, 6 (86 %) of 7 FMF AIP patients showed homogeneous enhancement, whereas only 3 chronic pancreatitis patients (25 %) and none of the pancreatic cancer patients showed homogeneous enhancement. None of the FMF AIP patients showed upstream main pancreatic duct dilatation greater than 5 mm or proximal pancreatic atrophy. It was concluded that for patients with a pancreatic mass, if their radiological images show homogeneous

enhancement on the portal venous phase, the absence of significant upstream main pancreatic duct dilatation greater than 5 mm, and the absence of proximal pancreatic atrophy, then conducting further evaluations should be considered to avoid performing unnecessary surgery [313].

The purposes of one study were to define the pancreatic enhancement of autoimmune pancreatitis at dual-phase CT and to compare it with that of pancreatic carcinoma and a normal pancreas. Dual-phase CT scans of 101 patients (43 with autoimmune pancreatitis, 13 cases of which were focal; 33 with pancreatic carcinoma, and 25 with a normal pancreas) were evaluated. One radiologist measured the CT attenuation of the pancreatic parenchyma and pancreatic masses in both the pancreatic and hepatic phases of imaging. The mean CT attenuation value of the pancreatic parenchyma in patients with autoimmune pancreatitis was compared with that in patients with a normal pancreas. The mean CT attenuation value of the focal masses in the focal form of autoimmune pancreatitis was compared with that of carcinomas. In the pancreatic phase, the mean CT attenuation value of the pancreatic parenchyma in patients with autoimmune pancreatitis was significantly lower than that in patients with a normal pancreas (autoimmune pancreatitis, 85 HU; normal pancreas, 104 HU). In the hepatic phase, however, the mean CT attenuation values were not significantly different (autoimmune pancreatitis, 96 HU; normal pancreas, 89 HU). In the pancreatic phase, the mean CT attenuation value of the mass in autoimmune pancreatitis was not significantly different from that of carcinoma (autoimmune pancreatitis, 71 HU; carcinoma, 59 HU), but in the hepatic phase, the value was significantly higher than that of carcinoma (autoimmune pancreatitis, 90 HU; carcinoma, 64 HU). It was concluded that at dual-phase CT, the enhancement patterns of the pancreas and pancreatic masses in patients with autoimmune pancreatitis are different from those of pancreatic carcinoma and normal pancreas [314].

PET-CT for differential diagnosis

One study was conducted to evaluate the clinical usefulness of PET/CT in differentiating autoimmune pancreatitis from pancreatic cancer. It was analyzed the cases of 17 patients with autoimmune pancreatitis and atypical pancreatic imaging findings who underwent integrated PET/CT. The PET/CT findings on the 17 patients with autoimmune pancreatitis were compared with those of 151 patients with pancreatic cancer. Fluorine-18 FDG uptake by the pancreas was found in all patients with autoimmune pancreatitis and in 82 percent (124/151) of patients with pancreatic cancer. Diffuse uptake by the pancreas was significantly more frequent in patients with autoimmune pancreatitis (53 % vs 3 %). FDG uptake by the salivary glands and kidneys was seen only in patients with autoimmune pancreatitis, the former reaching statistical significance. Follow-up PET/CT after steroid therapy was performed for eight patients with autoimmune pancreatitis. After steroid therapy, none of the patients had intense FDG uptake by the pancreas or extrapancreatic organs. It was concluded that in difficult cases, at PET/CT the presence of diffuse uptake of FDG by the pancreas or concomitant extrapancreatic uptake by the salivary glands can be used to aid in differentiation of autoimmune pancreatitis and pancreatic cancer [315].

Positrone emission tomography

The aim of one study was to analyze the usefulness of positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) in the evaluation of distribution and activity of systemic lesions of AIP during steroid therapy. Eleven cases of autoimmune pancreatitis had their FDG-PET images evaluated before and 3 months after steroid therapy and another 2 cases only before therapy. AIP activity was determined by the level of serum markers, IgG and IgG4, and compared with findings of PET. In all 13 cases of AIP, a moderate to intense level of FDG accumulation was recognized in the pancreatic lesion before steroid therapy. Of 13 patients, 11 (85 %) showed FDG accumulation in the multiple organs, such as mediastinal

and other lymph nodes, salivary gland, biliary tract, prostate, and aortic wall. In 11 patients who underwent PET before and after steroid therapy, FDG accumulation was diminished in almost all systemic lesions, with a mean of maximum standardized uptake value (SUV_{max}) in the pancreatic lesion from 5.1 to 2.7. Similar to the SUV level, serum IgG and IgG4 were decreased in most of the cases after steroid therapy. It was concluded that FDG-PET is an effective modality to evaluate the response of steroid therapy and the distribution and activity of various systemic lesions of autoimmune pancreatitis [316].

Missdiagnosis

Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of the pancreas that is increasingly encountered worldwide. It has generated considerable interest, in part because the inflammatory process usually responds dramatically to corticosteroid therapy. The most common presentation mimics that of pancreatic cancer; thus, a correct diagnosis of AIP can avoid major surgery. However, the diagnosis is challenging, because its incidence is far lower than that of the diseases it mimics and there is no single diagnostic clinical feature or test that can identify the full spectrum of AIP. Therefore, there has been increasingly encountering patients misdiagnosed as having AIP. The misdiagnosis typically occurs in three scenarios:

- treatment of pancreatic or biliary malignancy with corticosteroids and/or immunomodulators
- treatment of chronic abdominal pain with corticosteroids and/or immunomodulators
- performance of operative resection for autoimmune disease.

This growing clinical problem must be reinforced by use of published guidelines for the diagnosis and management of autoimmune pancreatitis [317].

Concomittant cancer

An asymptomatic 59-year-old man underwent pancreatoduodenectomy for a pancreatic mass that was discovered during a health check-up. Histopathology indicated typical features of CLPSP) or autoimmune pancreatitis along with the presence of abundant IgG4-positive plasma cells throughout the mass. A small invasive ductal adenocarcinoma was observed in the center of the area affected by LPSP [318].

Case reports

IgG4-related sclerosing disease is a distinctive mass-forming lesion with frequent systemic involvement, most frequently the pancreas, salivary glands, and lacrimal glands. One report described a case manifesting with a previously unrecognized form of central nervous system involvement. The 37-year-old man presented with signs and symptoms of spinal cord compression at the thoracic level 9. Magnetic resonance imaging revealed an elongated dural mass extending from the fifth to tenth thoracic vertebra. Laminectomy and excision of the mass revealed dura expanded by a dense lymphoplasmacytic infiltrate accompanied by stromal fibrosis and phlebitis. IgG4+ plasma cells were increased and the proportion of IgG4+/IgG+ plasma cells was 85 percent. The patient also had a 1-year history of bilateral submandibular swelling due to chronic sialadenitis. Thus, IgG4-related sclerosing pachymeningitis represents a new member of the IgG4-related sclerosing disease family affecting the central nervous system. It seems that at least a proportion of cases described in the literature as idiopathic hypertrophic pachymeningitis belong to this disease, especially as

some patients have other clinical manifestations compatible with IgG4-related sclerosing disease, such as cholangitis and orbital pseudotumor [319].

A 38-year old man presented himself for further clarification of a previously discovered circumscribed stenosis of the pancreatic duct. He had experienced several episodes of pancreatitis characterized by abdominal pain and increased lipase values. An endoscopic retrograde cholangiopancreatography demonstrated a "double duct" sign with corresponding stenosis of the bile and pancreatic ducts. No space-occupying mass was identified. There was no evidence of chronic pancreatitis. Post-inflammatory stenosis of the pancreatic duct was suspected. As the patient requested definitive diagnosis Whipple's operation was performed. It confirmed that the changes were benign. Histologic examination revealed changes of an autoimmune pancreatitis. It was concluded that circumscribed changes in the pancreatic duct, especially in young patients, should be clarified with all modern invasive and noninvasive modes of investigation to exclude with certainty a malignancy and avoid unnecessary resection [320].

It was reported a case of a man who simultaneously presented with autoimmune pancreatitis associated with retroperitonal fibrosis, and a lesion of the extrapancreatic bile duct, with total response to corticosteroid treatment for 4 months and absence of recurrence after 24 months of follow-up. Autoimmune pancreatitis is a kind of chronic pancreatitis that is probably a part of a systemic autoimmune disease, with retroperitoneal fibrosis and extrapancreatic bile duct lesion being the most commonly associated extrapancreatic lesions. A correct diagnosis and early treatment of this disease may aid in the total resolution of lesions, especially in cases with a low activity grade [321].

HEREDITARY PANCREATITIS

Patients with hereditary pancreatitis bear a high risk of pancreatic adenocarcinoma, but their life expectancy remains unknown. The objective of the study was to assess whether the high risk of cancer decreases survival. Inclusion criteria were the presence of a PRSS1 mutation with pancreatic symptoms or chronic pancreatitis in at least two first-degree relatives or three second-degree relatives without another cause. Survival rates were assessed according to risk factors. Excess mortality compared with the general French population was calculated for two periods (20-50 and 50-70 years), according to several risk factors. The cohort comprised 189 patients. PRSS1 mutations were found in 66 percent. A total of 19 patients died at the median age of 60. In all, 10 deaths were attributable to hereditary pancreatitis, including 8 to pancreatic adenocarcinoma. Median overall survival for the whole cohort was 74 years (95 % confidence interval 71 to 79). The presence of R122H mutation, gender, tobacco consumption in patients older than 18 years, and diabetes mellitus were not associated with differences in survival. Only patients with pancreatic cancer had decreased survival. Excess mortality risk compared with the general population was 0.02 percent between 20 and 50 years, and 0.61 percent between 50 and 70 years (a statistically non-significant difference). Gender, R122H mutation, diabetes, and tobacco use were not associated with excess mortality in these two periods. The authors concluded that despite their high risk of cancer, patients with hereditary pancreatitis do not have excess mortality risk compared with the general population, irrespective of gender, tobacco use, or diabetes mellitus [322].

The N34S mutation in the serine protease inhibitor Kazal type I (SPINK1) gene has been associated with chronic pancreatitis. Clinical data about the phenotypic expression of alcoholic chronic pancreatitis with the N34S variant are limited. The prevalence of the N34S mutation in patients with chronic pancreatitis and healthy individuals from Eastern Europe is unknown. It was studied Romanian patients with chronic pancreatitis and investigated the clinical presentation in patients with N34S mutation. The SPINK1 N34S variant was analysed in 94 chronic pancreatitis patients and 96 healthy controls by an allele specific PCR method and a restriction fragment length polymorphism method. A meta-analysis was conducted with previous N34S association studies. The clinical course of alcoholic pancreatitis was evaluated according to the severity criteria of the M-ANNHEIM classification system of chronic pancreatitis. A heterozygous N34S mutation was found in 1 of 96 healthy individuals (1 %) and in 4 of 80 patients (5 %) with alcoholic chronic pancreatitis. The meta-analysis confirmed the status of N34S as a risk factor for the development of alcoholic chronic pancreatitis (odds ratio 5.3). However, the clinical course of the disease was similar in patients with and without N34S mutation. It was thus concluded that N34S mutation is a weak risk factor for alcoholic chronic pancreatitis [323].

PRSS1 and SPINK1 are 2 important genes in the defense mechanism guarding against the development of pancreatitis. One study aimed to evaluate the prevalence of PRSS1 and SPINK1 mutations and to explore the presence of any ethnic specificity in Korean patients. A total of 47 patients from 40 families including 37 patients with idiopathic pancreatitis and 10 patients with familial pancreatitis were prospectively enrolled. Fifty healthy controls were included for analysis of SPINK1 IVS3+2T site. PRSS1 mutations were observed in 6 patients from 2 families and SPINK1 mutations in 13 patients from 11 families, respectively. In case of SPINK1 mutations, N34S and IVS3+2T>C were identified in 3 and 11 patients, respectively, including one with compound N34S/IVS3+2T>C heterozygote. The prevalence of SPINK1 IVS3+2T>C mutations was 27 percent among 41 patients without PRSS1 mutations, whereas the prevalence among 50 healthy controls was 0 percent. Only PRSS1 R122H was identified. Late onset of symptoms at the age of 36 years and absence of symptoms at the age of 47 years were observed in 2 patients with PRSS1 mutations. It was concluded that PRSS1 and SPINK1 mutations were not rare in Korean patients with idiopathic and familial

pancreatitis. SPINK1 IVS3+2T>C was a prevalent mutation in this population [324].

Case report

A 72-year-old woman with Mikulicz disease with pathogically proven sclerosing sialadenitis showed systemic abnormal F-18 FDG uptake in the bilateral lacrimal and submandibular glands, pancreas, abdominal aortic wall, and a retroperitoneal fibroid mass on PET/CT scan, with marked elevation of the serum IgG4 level. This case supports Mikulicz disease being included as 1 of the disorders associated with a new clinical entity of systemic IgG4-related plasmacytic syndrome. A whole-body FDG-PET/CT scan can be expected as a useful tool for detecting systemic involvement in systemic IgG4-related plasmacytic syndrome [325].

PANCREATIC CANCER

Classification of pancreatic tumors

The recent sequencing of the pancreatic cancer genome provides unprecedented insight into the fundamental nature of this deadly malignancy. Although much work still needs to be done, a molecular classification of neoplasms of the pancreas is emerging. Molecular genetics have been used to identify unique clinical subtypes of pancreatic cancer, to guide the clinical diagnosis of pancreatic tumors, and to identify targeted therapies for select pancreatic neoplasms. A new classification does not ignore previous histology-based classification systems but instead embraces them, creating an integrated histological-molecular classification [326].

Demography and epidemiology

Statistics in theory

Actuarial 5-year survival rates exceeding 20 percent are often reported for patients undergoing pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas. In contrast, when actual long-term patient survival rates following pancreatoduodenectomy for ductal adenocarcinoma have been reported, they have been disappointingly lower than the optimistic survival results predicted by those studies using actuarial analysis. This discrepancy between actuarial estimation of patient survival and actual patient survival following pancreatoduodenectomy for pancreatic ductal adenocarcinoma has been explained away by some puckish observers as resulting from "the magic of Kaplan-Meier." A more precise explanation of the discrepancy lies in the fact that Kaplan-Meier calculations are statistical estimates and become artificially inflated either if shorter-term survival patients are also included in the analysis, or if patients are lost to follow-up. Accordingly, actual survival rates represent the gold standard for measuring operative success, particularly in long-term studies [327].

Importance of race

African Americans have a poorer survival from gastrointestinal cancers. It was hypothesized that socioeconomic status may explain much of this disparity. Four years of population-based Medicare and Medicaid administrative claims files were merged with the Michigan Tumor Registry. Data were identified for 18,260 patients with colorectal (n=13,001), pancreatic (n=2,427), gastric (n=1,739), and esophageal (n=1,093) cancer. Three outcomes were studied: the likelihood of late stage diagnosis, the likelihood of surgery after diagnosis, and survival. Bivariate analysis was used to compare stage and operation between African-American and Caucasian patients. In unadjusted analyses, relative to Caucasian patients, African-American patients with colorectal and esophageal cancer were more likely to present with metastatic disease, were significantly less likely to have surgery, and were less likely to survive during the study period. No racial differences in survival were observed among patients with esophagus, gastric, or pancreatic cancer. It was concluded that race has little influence on survival of patients with pancreatic cancer [328].

Sweden

The aim of one study was to characterise the familial association of pancreatic cancer with other malignancies. Relative risks (RRs) of pancreatic cancer according to family history of cancer were calculated using the updated Swedish Family-Cancer Database, which includes

over 11.5 million individuals. Estimates were based on Poisson regression. RRs of tumours for individuals with a parental history of pancreatic cancer were also estimated. The risk of pancreatic cancer was elevated in individuals with a parental history of cancers of the liver (RR 1.41; 95 % confidence interval 1.10 to 1.81), kidney (RR 1.37; 95 % confidence interval 1.06 to 1.76), lung (RR 1.50; 95 % confidence interval 1.27 to 1.79) and larynx (RR 1.98; 95 % confidence interval 1.19 to 3.28). Associations were also found between parental history of pancreatic cancer and cancers of the small intestine, colon, breast, lung, testis and cervix in offspring. There was an increased risk of pancreatic cancer associated with early-onset breast cancer in siblings. Pancreatic cancer aggregates in families with several types of cancer. Smoking may contribute to the familial aggregation of pancreatic and lung tumours, and the familial clustering of pancreatic and breast cancer could be partially explained by inherited mutations in the BRCA2 gene [329].

Danmark

It was reported the incidence rates of pancreatic cancer in Denmark during 61 years of data registration, from 1943 to 2003 and it was calculated age-standardized, period-specific incidence rates of pancreatic cancer. A total of 32,654 incident cases of pancreatic cancer were evaluated (male-female ratio, 1.4). The age-standardized incidence rate of pancreatic cancer increased steadily in the beginning of the study period from 3.75/100,000 person-years in 1943 to 1947 to the maximum of 9.96/100,000 person-years in 1968 to 1972 among men and from 2.95 in 1943 to 1947 to the maximum of 7.04 in 1978 to 1982 among women. The incidence rates declined between 1968 to 1972 and 1988 to 1992 for men and between 1978 to 1982 and 2003 for women. More than 40 percent of the tumors were located in the head of the pancreas; 14 percent were localized, 21 percent were regionally spread, and 36 percent were metastatic at the time of diagnosis. During the period 1978 to 2003, the percentages of histologically or cytologically verified adenocarcinomas remained relatively steady, approximately 30 percent [330].

France

In 2006, a total number of 149,000 cancer deaths were observed in France, 88,500 in the male population and 60,500 in the female population. In 2005, the number of new diagnoses of cancer is estimated to be 319,000, 183,000 among men and 136,000 among women. Age-standardised mortality rates are decreasing for most frequent cancer sites, at least in recent years, the main exceptions being lung in the female population, and pancreas in both male and female populations [331].

Korea

Using the population-based cancer registry in Jejudo, it was found that Jejudo had lower incidence in stomach cancer than other regions in Korea. The aim of one study was to evaluate reasons for this difference. Citrus is the leading agricultural production in Jejudo, suggesting that lower cancer incidence in Jejudo could be explained by citrus fruit intake. It was evaluated this hypothesis with quantitative systematic review (QSR). Stomach cancer incidence was significantly lower, with a summary odds ratio (SOR) after QSR of 0.72. In addition, the SOR of pancreatic cancer tended to be lower at 0.83 (95 % confidence interval 0.70 to 0.98). It was suggested that lower cancer incidence in Jejudo could be explained by intake of citrus fruits [332].

Arctic pancreatic cancer

Little information is available on the incidence and mortality of cancer among the Aboriginal population in the Province of Québec, Canada. Cancer was likely rare in this population

historically, but recent life-style changes suggest that this may no longer be the case. The purpose of this study was to estimate incidence and mortality rates among Aboriginal people living on reserves and in northern villages in Québec during the period 1988-2004, and to compare these estimates with those of the general population. Aboriginal people were identified based on geographic residence codes. Population data were taken from the Canadian census of 1991, 1996 and 2001. Incidence and mortality rates were calculated and age-standardized according to the World Standard Population. The Aboriginal incidence and mortality rates for cancer, all sites combined, was 322 per 100,000 (95 % confidence interval 305 to 339) and 160 per 100,000 (95 % CI 148-173), respectively. These rates are not significantly different from those of the general population of Québec. However, there are differences according to cancer site and sex. Aboriginal men had a higher risk for liver, lung and kidney cancers and a lower risk for prostate, bladder, leukemia and non-Hodgkin's lymphoma cancers, whereas Aboriginal women had a higher risk for colorectal, lung, cervix and kidney cancers, and a lower risk for breast, uterus, bladder, brain, leukemia, stomach and pancreas cancers [333].

Nenetskij Avtonomnyj Okrug (NAO), a part of Arkhangelskaja Oblast in north-west Russia, has a population of 42,000 inhabitants. The central oncological hospital of the oblast registers all new cases of cancer. All new cases recorded in the study period among official residents of NAO were included in the study, except for secondary malignant neoplasm, cases revealed by autopsy and cancers diagnosed within 6 months of a previous cancer diagnosis. The census and annual sex and age-group-specific population figures for NAO were obtained from the regional statistics office. Crude and age-adjusted incidence rates (to the world standard population) were estimated. The average crude cancer incidence per year was 204/100,000 among men and 194/100,000 among women. Adjusted for age, the incidence was 322/100,000 and 182/100,000, respectively. The most frequent primary site of cancer was trachea, bronchus and lung, which constituted 17 percent of all cases (of which 87 % were among men), followed by stomach cancer (13 %). Breast cancer constituted 18 percent of all cases among women. The results are consistent with reports of a low cancer risk among women compared with men in Russia and compared with women in Western countries and with results that point out that public health measures are needed to curb the lung cancer epidemic among men in Russia. The high risks of pancreas, kidney and oesophagus cancers among men should be investigated further [334].

Pancreatic compared to peripancreatic cancers

Carcinomas co-occur in the pancreas, extrahepatic bile ducts, and ampulla of Vater. It was investigated whether cancers originating in these sites represent a field effect similar to that observed in the lung and upper aerodigestive tract. To determine whether a field effect for carcinogenesis exists in the ampulla of Vater, extrahepatic bile ducts, gallbladder, and pancreas data were obtained from National Cancer Institute's Surveillance Epidemiology and End Results Program from 1973 through 2005. Cases were compared by age frequency density plots, age-specific incidence rates, and logarithmic plots of the age-specific incidence rates and age of diagnosis. Incidence rates were 11.71, 1.43, 0.88, and 0.49 per 100,000 persons at risk for pancreatic, gallbladder, extrahepatic bile ducts, and ampullary carcinomas, respectively. Age frequency density plots were congruent for cancers originating in all 4 sites. Logarithmic plots of the age-specific incidence rates with age of diagnosis produced parallel linear rate patterns for the 4 sites indicative of similar populations for tumor development. However, density and logarithmic plots of pancreatic endocrine carcinomas, a tumor of different cellular differentiation and carcinogenic pathway, served as a comparison. The endocrine carcinomas showed a different age distribution and nonparallel rate patterns with ductal carcinomas. It was concluded that carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla have a common embryonic cellular ancestry, differentiation pathways, mucosal histologic patterns, and population-related tumor

development indicating a field effect in carcinogenesis. Parallel linear rate patterns indicate that the rate of cancer development is similar in all four sites even though the absolute incidence rates vary and, regardless of location, the ductal epithelium is equally susceptible to malignant transformation. If carcinogenic pathways to cancer are similar, then the different incidence rates seen clinically may depend on the relative surface area of the ductal system in these sites. Pancreatic cancers are most common because the surface area of the pancreas' ductal system is greater than that of the gallbladder, extrahepatic bile ducts, and ampulla [335].

Death at home

The purpose of one study was to confirm the recent trends in home deaths among cancer deaths in Osaka Prefecture. The number of home deaths (the proportion of home deaths among cancer deaths) has continuously increased from 875 (4.6 %) in 1995 to 1,544 (6.6 %) in 2006. The proportions increased gradually in most second-level medical-care areas. Since 2004, the proportion in the Toyono medical-care area has increased rapidly and reached 10.6 percent in 2006. The proportions of cancers of the lung, colorectum, stomach, pancreas and breast gradually increased from around 5 percent in 1995 to around 7 percent in 2006 [336].

Etiological factors

Although mounting evidence suggests that insulin resistance is involved in pancreatic carcinogenesis, few epidemiologic studies have comprehensively investigated the role of lifestyle factors influencing this metabolic disorder in the etiology of pancreatic cancer. It was now sought to examine this problem in a case-control study conducted in 1994-1998 in Minnesota. Cases (n=186), aged 20 years or older, were ascertained from all hospitals in the metropolitan area of the Twin Cities and the Mayo Clinic; from the latter, only cases residing in the Upper Midwest of the United States were recruited. Controls (n=554) were randomly selected from the general population and frequency matched to cases by age (within 5 years) and sex. Odds ratios (OR) and 95 % confidence intervals were estimated using unconditional logistic regression. After adjustment for confounders, physical activity was associated with a reduced risk, but this protective effect was confined to light activity and moderate activity only (OR 0.55, 95 % confidence interval 0.30 to 0.97; and OR 0.51, 95 % confidence interval 0.28 to 0.93, for highest vs. lowest quartile, respectively). An increased risk was found for dietary intakes of energy and fat but was statistically significant for saturated and polyunsaturated fat only. Of note, no appreciable difference in the magnitude of the associations existed between saturated, monounsaturated, and polyunsaturated fat. Compared with individuals in the lowest quartile of fiber intake, the risk was approximately halved for those in the third (OR 0.49, 95 % confidence interval 0.26 to 0.94) and the highest quartile (OR 0.52, 95 % confidence interval 0.21 to 1.30). The study lends support to the hypothesis that dietary and other lifestyle factors influencing insulin resistance modulate pancreatic cancer risk [337].

Read meat and risk of cancer

High intake of meat, particularly red and processed meat, has been associated with an increased risk of a number of common cancers such as breast, colorectum, and prostate in many epidemiological studies. Heterocyclic amines (HCAs) are a group of mutagenic compounds found in cooked meats, particularly well-done meats. HCAs are some of most potent mutagens detected using the Ames/salmonella tests and have been clearly shown to induce tumors in experimental animal models. Over the past 10 years, an increasing number of epidemiological studies have evaluated the association of well-done meat intake and meat

carcinogen exposure with cancer risk. The results from these epidemiologic studies were evaluated and summarized in this review. The majority of these studies have shown that high intake of well-done meat and high exposure to meat carcinogens, particularly HCAs, may increase the risk of human cancer [338].

Smoking

Cigarette smoking doubles the risk of pancreatic cancer, and smoking accounts for 20 to 25 percent of pancreatic cancers. The recent sequencing of the pancreatic cancer genome provides an unprecedented opportunity to identify mutational patterns associated with smoking. It was previously sequenced >750 million bp DNA from 23,219 transcripts in 24 adenocarcinomas of the pancreas (discovery screen). In this previous study, the 39 genes that were mutated more than once in the discovery screen were sequenced in an additional 90 adenocarcinomas of the pancreas (validation screen). Now, it was compared the somatic mutations in the cancers obtained from individuals who ever smoked cigarettes (n=64) to the somatic mutations in the cancers obtained from individuals who never smoked cigarettes (n=50). When adjusted for age and gender, analyses of the discovery screen revealed significantly more nonsynonymous mutations in the carcinomas obtained from ever smokers (mean, 53 mutations per tumor) than in the carcinomas obtained from never smokers (mean, 38.5). The difference between smokers and nonsmokers was not driven by mutations in known driver genes in pancreatic cancer (KRAS, TP53, CDKN2A/p16, and SMAD4), but instead was predominantly observed in genes mutated at lower frequency. No differences were observed in mutations in carcinomas from the head versus tail of the gland. Pancreatic carcinomas from cigarette smokers harbor more mutations than do carcinomas from never smokers [339].

A meta-analysis of observational studies on association between cigarette smoking and pancreatic cancer was performed to focus, particularly, on the role of the studies' quality in affecting meta-analysis results. A bibliographic search was carried out on PubMed and EMBASE databases until February 15, 2008. Key words were "pancreatic neoplasms," "pancreatic cancer," "smoking," "smoke," "cigarette," "case-control studies," and "cohort studies." Studies about cigarette smoking and pancreatic cancer were selected and assessed on quality. Six cohort studies and 24 case-control studies were selected, with median quality scores of 8 (range, 3) and 10 (range, 8), respectively. Pooled case-control studies' odds ratio (OR) and cohort studies' risk ratio were, respectively, 1.45 (95 % confidence interval 1.33 to 1.57) and 1.78 (95% CI, 1.64-1.92). After stratifying for quality scoring, high-quality-scored case-control studies yielded an odds ratio of 1.38 (95 % confidence interval 1.27 to 1.49), whereas the others gave an odds ratio of 1.52 (95 % confidence interval 1.34 to 1.73). The results of meta-analysis for cohort studies showed a risk ratio of 1.74 (95 % confidence interval 1.61 to 1.90) and of 2.10 (95 % confidence interval 1.64 to 2.67), respectively, for high- and low-quality score studies. It was thus concluded that here is evidence that cigarette smoking is an important risk factor for pancreatic cancer, but the estimate of the association greatly relies on the studies' quality [340].

To evaluate the effects of nicotine and cigarette smoke exposure on mice submitted to 7,12-dimethylbenzanthracene (DMBA) model of pancreatic carcinogenesis. One hundred fourteen male mice were divided into the DMBA-n and DMBA-s groups: the DMBA-n group was given 2 mg/kg per dose of nicotine subcutaneously for 45 days, and the DMBA-s group was exposed to 100 mg/m^3 of cigarette smoke. At day 16, 1 mg of DMBA crystals was implanted in the pancreatic head of both groups. Euthanasia was performed in all mice 30 days after the surgery. The specimens were evaluated according to the following criteria: normal ducts, reactive hyperplasia, pancreatic intraepithelial neoplasm 3 (PanIN-3), and carcinoma. The frequency of PanIN in the 3 groups was almost the same when considering the higher-grade

lesions: controls (67 %), DMBA-s (67 %), and DMBA-n (44 %). Pancreatic adenocarcinoma has a higher frequency in the DMBA-n group (52 %) than in the controls (17 %) and DMBA-s (13 %) groups. The DMBA-s group has the highest score of PanIN-3 (40 %). The differences among the groups were statistically significant. It was concluded that nicotine but not cigarette smoke promotes pancreatic DMBA carcinogenesis in mice. Pancreatic adenocarcinomas and PanINs have the same phenotypic appearance as those that occur in humans [341].

Alcohol and smoking

The association between alcohol consumption and pancreatic cancer is not clear. One study investigates different prediagnostic measurements of alcohol consumption, a laboratory marker (gamma-glutamyltransferase), and a score measuring alcohol addiction (Mm-MAST), in relation to the risk of pancreatic cancer. Furthermore, the study investigated whether smoking and alcohol consumption interact with each other, or if the risk of pancreatic cancer associated with these factors is modified by obesity or weight gain. A cohort of 33,346 subjects provided prediagnostic information on the above factors. During a mean follow-up of 22 years, 183 cases of pancreatic cancer occurred. The highest gamma-GT quartile was associated with a high risk of pancreatic cancer (RR = 2.15, 95% CI = 1.34-3.44), and this association was even stronger in subjects that reported a previous weight gain (RR = 3.61, 95% CI = 1.29-10.09). A high Mm-MAST score was also associated with pancreatic cancer ($p = 0.02$). Current smoking was associated with pancreatic cancer (RR = 2.34, 95% CI = 1.60-3.43), and obese smokers had an even higher risk (RR = 7.45, 95% CI = 1.65-33.64). Conclusion: High alcohol intake is associated with subsequent risk of pancreatic cancer and this risk may be higher following weight gain. The risk associated with smoking may be even higher in obese subjects [342].

Life-style factors

Smoking, alcohol use, diet, body mass index, and physical activity have been studied independently in relation to pancreatic cancer. It was generated a healthy lifestyle score to investigate their joint effect on risk of pancreatic cancer. In the prospective National Institutes of Health-AARP Diet and Health Study, a total of 450 416 participants aged 50 to 71 years completed the baseline food frequency questionnaire (1995-1996) eliciting diet and lifestyle information and were followed up through December 31, 2003. It was identified 1057 eligible incident pancreatic cancer cases. Participants were scored on 5 modifiable lifestyle factors as unhealthy (0 points) or healthy (1 point) on the basis of current epidemiologic evidence. Participants received 1 point for each respective lifestyle factor: nonsmoking, limited alcohol use, adherence to the Mediterranean dietary pattern, body mass index ($\geq$18 and <25), or regular physical activity. A combined score (0-5 points) was calculated by summing the scores of the 5 factors. Compared with the lowest combined score (0 points), the highest score (5 points) was associated with a 58 percent reduction in risk of developing pancreatic cancer in all participants (relative risk, 0.42; 95% confidence interval, 0.26 to 0.66). Scores of less than 5 points were associated with 27 percent of pancreatic cancer cases in our population. Findings from this large study suggest that having a high score, as opposed to a low score, on an index combining 5 modifiable lifestyle factors substantially reduces the risk of developing pancreatic cancer [343].

Carbohydrate intake

Diets with high glycemic index and glycemic load have been associated with insulin resistance. Insulin resistance has been implicated in the etiology of pancreatic cancer. It was prospectively investigated the associations between glycemic index, carbohydrates, glycemic load, and available carbohydrates dietary constituents (starch and simple sugar) intake and

the risk of pancreatic cancer. It was followed the participants in the NIH-AARP Diet and Health Study from 1995/1996 through 2003. A baseline self-administered food frequency questionnaire was used to assess the dietary intake and exposure information. A total of 1,151 exocrine pancreatic cancer cases were identified from 482,362 participants after excluding first-year of follow-up. There were no associations between glycemic index, total or available carbohydrates, gycemic load, and pancreatic cancer risk. Participants with high free fructose and glucose intake were at a greater risk of developing pancreatic cancer. There were no statistically significant interactions by body mass index, physical activity, or smoking status. The results do not support an association between glycemic index, total or available carbohydrate intake, and glycemic load and pancreatic cancer risk. The higher risk associated with high free fructose intake needs further confirmation and elucidation [344].

Fructose

Using fructose dehydrogenase-catalyzed conversion of d-fructose to 5-ketofructose, followed by quantitation of MTT [3-(4,5-dimethylthiaze-syl)-2,5-diphenyltetrazolium bromide] formazan production by direct spectrophotometry, an assay to measure serum fructose concentration was developed, and assay sensitivity and specificity were tested. Validity of the assay was confirmed by gas chromatography-mass spectroscopy, and the assay was tested in healthy subjects and pancreatic cancer patients. The assay was highly specific, exhibiting no cross-reactivity with other sugars. Mean serum fructose concentration in fasting healthy volunteers was 1.9 + 0.4 mM and after ingestion of a fructose and glucose-containing drink rose to 16.3 + 1.2 mM at 15 minutes and peaked at 30 minutes when serum fructose was 17.2 + 1.1 mM. Mean fasting serum fructose level was significantly higher at 5.7 + 2.5 mM in patients with pancreatic cancer than those with no pancreatic cancer. The fructose dehydrogenase-based enzymatic assay correlated highly with gas chromatography-mass spectroscopic analysis of serum fructose with a correlation coefficient of 0.94. It was concluded that measurement of serum fructose concentration may provide insight into the relationship between refined fructose intake and diseases including pancreatic cancer [345].

Citrus fruits

The purpose of one systematic review was to investigate the association between dietary intake of citrus fruits and pancreatic cancer risk. The authors searched electronic databases and the reference lists of publications of studies addressing diet and pancreatic cancer up to December 2007. All of the epidemiological studies that obtained individual data on dietary intake of citrus fruits and presented risk estimates of the association between intake of citrus fruits and risk of pancreatic cancer were identified and included. Using general variance-based methods, study-specific odds ratios (ORs)/relative risk and associated confidence interval (CI)/SE for highest versus lowest intake of citrus fruits level were extracted from each article. Nine articles including 4 case-control studies and 5 cohort studies proved eligible. Overall summary OR using random effect model suggested an inverse association in risk of pancreatic caner with intake of citrus fruits (summary odds ratio, 0.83) with large heterogeneity across studies. It was concluded that pooled results from observational studies showed an inverse association between intake of citrus fruits and the risk of pancreatic cancer, although results vary substantially across studies, and the apparent effect is restricted to the weaker study design (case-control studies) [346].

Pollution

To describe the mortality profile of the population resident in the polluted area of national concern "Laguna di Grado e Marano" Friuli-Venezia-Giulia region, in the period 1997-2001 and to examine mortality temporal trends between 1981 and 2001 a small-area epidemiological study based on descriptive statistics, socioeconomic deprivation variables,

analysis of spatial heterogeneity disease mapping and time trend analysis was carried out. Compared to regional averages, standardised mortality ratios in the region were significantly higher for lung and stomach cancer in men and for ovarian cancer in women. Standardised mortality ratios were instead significantly lower for all causes of death (8.7 %), respiratory and cardiovascular diseases, liver (51%) and pancreas (47 %) cancer in men and for cardiovascular diseases in women. These results did not change after adjustment by socioeconomic status [347].

Radon

It was correlated radon exposure with the incidence of pancreatic cancer and to ascertain the influence of race in this correlation. Age-standardized incidence rates (SIRs) of pancreatic cancer from 1992 to 2002, segregated by race, were obtained from the Surveillance, Epidemiology, and End Results database. The mean radon levels for each county were obtained from the Environmental Protection Agency map, which assigns each county to 1 of 3 categories based on radon potential. The SIRs of pancreatic cancer in the United States ranged from 1.4 to 21.8/100,000 person-years. The highest rates for whites (19.6/100,000 person-years) and American Indians (594/100,000 person-years) were found in Guadalupe County, New Mexico; for African Americans (4845/100,000 person-years) in Worth County, Iowa; and for Asian Americans (3177/100,000 person-years) in Monroe County, Iowa. There was an insignificant correlation between radon exposure and overall incidence of pancreatic cancer. A significant correlation existed between radon exposure and incidence of pancreatic cancer in African Americans, American Indians, and Asian Americans, but not in whites. The authors concluded that radon exposure may be a significant risk factor for pancreatic cancer in African Americans, American Indians, and Asian Americans [348].

Vitamine D

Experimental evidence suggests that vitamin D has anticarcinogenic properties; however, a nested case-control study conducted in a population of male Finnish smokers found that higher 25-hydroxyvitamin D [25(OH)D], the best indicator of vitamin D status as determined by the sun and diet, was associated with a significant 3-fold increased risk for pancreatic cancer. It was conducted a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Screening Trial cohort of men and women 55 to 74 years of age at baseline to test whether prediagnostic serum 25(OH)D concentrations were associated with pancreatic cancer risk. Between 1994 and 2006, 184 incident cases of pancreatic adenocarcinoma occurred (follow-up to 12 years). Two controls (n=368) who were alive at the time the case was diagnosed were selected for each case and matched by age, race, sex, and calendar date of blood draw (to control for seasonal variation). It was calculated odds ratios and 95 percent confidence intervals using conditional logistic regression, adjusting for smoking and body mass index. Vitamin D concentrations were not associated with pancreatic cancer overall (highest versus lowest quintile, >82 vs <46 nmol/L; odds ratio 1.45; 95 % confidence interval 0.66 to 3.15). However, positive associations were observed among subjects with low estimated annual residential solar UBV exposure, but not among those with moderate to high annual exposure. Thus, it was not confirmed the previous strong positive association between 25(OH)D and pancreatic cancer; however, the increased risk among participants with low residential UVB exposure was smilar [349].

Tocopherols

Evidence indicates that vitamin E has anticarcinogenic properties for gastrointestinal cancers; however, few studies have examined this with respect to exocrine pancreatic cancer. The objective was to examine whether vitamin E intake and serum alpha-tocopherol concentrations were prospectively associated with exocrine pancreatic cancer. It was

conducted a cohort analysis of prediagnostic vitamin E intake (4 tocopherols, 4 tocotrienols), serum alpha-tocopherol concentrations, and pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of male Finnish smokers aged 50-69 years at baseline. During follow-up from 1985 to 2004 (maximum: 19 years; median: 16 yeras), 318 incident cases were diagnosed among cohort participants with complete serum samples (n=29,092); 306 cases had complete dietary data (n=27,111). Higher alpha-tocopherol concentrations were associated with signifikant lower pancreatic cancer risk. Polyunsaturated fat, a putative prooxidant nutrient, modified the association such that the inverse alpha-tocopherol association was most pronounced in subjects with a high polyunsaturated fat intake. No associations were observed for dietary tocopherols and tocotrienols. The results support the hypothesis that higher alpha-tocopherol concentrations may play a protective role in pancreatic carcinogenesis in male smokers [350].

Nitrate in drinking water

A matched case-control and nitrate ecology study was used to investigate the association between mortality attributed to pancreatic cancer and nitrate exposure from Taiwan's drinking water. All pancreatic cancer deaths of Taiwan residents from 2000 through 2006 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 cases by gender, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case. Data on nitrate-nitrogen (NO_3-N) levels of drinking water throughout Taiwan were collected from Taiwan Water Supply Corporation. The municipality of residence for cancer cases and controls was assumed to be the source of the subject's nitrate exposure via drinking water. The adjusted odds ratios and confidence limits for pancreatic cancer death for those with high nitrate levels in their drinking water, as compared to the lowest tertile, were 1.03 (0.9-1.18) and 1.1 (0.96-1.27), respectively. The results of the present study show that there was no statistically significant association between the levels of nitrate in drinking water and increased risk of death from pancreatic cancer [351].

Perfluorooctanoate

Perfluorooctanoate and perfluorooctanesulfonate are used in many industrial products and have been widely detected in human blood. Both chemicals are associated with tumor development in animal studies, but data on carcinogenic potential in humans are sparse. It was investigated the association between plasma levels of perfluorooctanoate and perfluorooctanesulfonate and cancer risk within a prospective Danish cohort of participants with no previous cancer diagnosis at enrollment. From enrollment, between 1993 and 1997, and through, 2006, it was identified 713 participants with prostate cancer, 332 with bladder cancer, 128 with pancreatic cancer, and 67 with liver cancer in the entire cohort and it was selected a comparison subcohort of 772. Plasma concentrations of perfluorooctanoate and perfluorooctanesulfonate were measured in each participant by use of high-pressure liquid chromatography coupled to tandem mass spectrometry. It was found no clear differences in incidence rate ratios for these cancers in relation to plasma concentrations of perfluorooctanoate or perfluorooctanesulfonate. A 30-40 percent increase in risk estimates for prostate cancer was observed for the three upper quartiles of perfluorooctanesulfonate concentration compared with the lowest quartile. Plasma concentrations of perfluorooctanoate and perfluorooctanesulfonate in the general Danish population appear not to be associated with risk of prostate, bladder, pancreatic, or liver cancer [352].

Psoriasis

It was examined overall and specific cancer risks among Swedish subjects who had been hospitalised one or more times for psoriasis. A database was created by identifying such

patients from the Swedish Hospital Discharge Register and linking them with the National Cancer Registry. Follow-up of patients was carried out from the last hospitalisation through 2004. A total of 15 858 patients were hospitalised for psoriasis during 1965-2004, of whom 1408 developed cancer, giving an overall standardised incidence ratios (SIRs) of 1.33. A significant excess was noted for squamous cell skin cancer, and for cancers of the upper aerodigestive tract, oesophagus, stomach, liver, pancreas, lung, kidney and bladder as well as non-Hodgkin lymphoma. Many of these may reflect the effects of alcohol drinking and tobacco smoking [353].

Genetic aspects

Pancreatic cancer, like many other complex diseases, has genetic and environmental components to its etiology. It is likely that relatively common genetic variants with modest effects on pancreatic cancer risk play an important role in both familial and sporadic forms of the disease, either individually or in interaction with environmental factors. The relatively high frequency of such variants means that they could potentially explain a substantial portion of disease risk. In general, very few low-penetrance variants have been identified and those that have require replication in independent studies. Possible gene-environment interactions arising from these studies also require replication. More comprehensive approaches are needed to make progress, including global analyses of biologically sound pathways and genome-wide association studies. Large sample sizes are required to do this appropriately and multi-study consortia make this possible. A number of consortia of pre-existing studies have already been formed, and these will facilitate the identification of further low-penetrance variants and gene-environment interaction. However, these approaches do not substitute for the design of novel, sufficiently powered studies that apply uniform criteria to case selection, the acquisition of environmental exposure information, and to biological sample collection [354].

Hereditary pancreatic cancer comprises about 10 percent of pancreatic cancer cases. Multiple causative mutations have been identified. It was described a pancreatitis/pancreatic cancer family, which demonstrates pancreatitis and pancreatic cancer resulting from an uncharacterized mutation. Family members completed evaluations to determine signs of mutation status. Select patients were screened for mutations associated with hereditary pancreatic diseases. In generation II, 12 siblings exhibit 6 cases of pancreatitis, 3 pancreatic cancer, and 2 obligate carrier status. The average age at pancreatitis diagnosis of enrolled members is 33 years; average age at pancreatic cancer diagnosis is 59 years. There is no association with known cancer syndromes. Those affected generally present with mild epigastric pain, and CT scans demonstrate characteristic fatty infiltration of the pancreatic body and tail with sparing of the head and neck. Full sequence analysis of genes associated with hereditary pancreatic disease failed to demonstrate known mutations or polymorphisms. Based upon pedigree evaluation and preliminary DNA analysis, it was believed that the family members with pancreatitis/pancreatic cancer carry a novel genetic mutation resulting in hereditary pancreatitis. This mutation is autosomal dominant, expressed with high penetrance, and is part of a unique hereditary syndrome that significantly increases pancreatic cancer risk [355].

Screening

Several masses and premalignant lesions have been detected, but the detection of the first pancreatic cancer through an organised study of screening has yet to be published. There has been progress in risk stratification. A mutation in the palladin gene was found to segregate with the disease in a family with a clear predisposition for pancreatic cancer, though this has yet to be found in other such kindreds. This means that significant challenges

remain to be solved in screening for early pancreatic cancer. Risk stratification needs to be improved and high-risk patients included in research-based screening programmes. It will be impossible to confirm that screening can detect cancers early enough for curative treatment until the results of these prospective studies become available. Registries of high-risk patients may include hereditary pancreatitis kindreds, families from various general cancer syndromes and those with a specific predisposition for pancreatic cancer. Unfortunately, such registries may well also include families that have multiple cases of pancreatic cancer due to chance, unaffected members of the latter group having no elevated risk. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) recruits patients with at least two cases of pancreatic cancer or pancreatitis in first- or second-degree relatives. A family tree of at least three generations is produced. To avoid as many random clusters as possible, only families which are consistent with autosomal dominant inheritance of either pancreatic cancer or pancreatitis are included as having familial pancreatic cancer (FPC) or hereditary pancreatitis (HP). When the participants consent, EUROPAC also tests for mutations in PRSS1 for HP families and BRCA2 for FPC families. If cases of melanoma are reported, the CDKN2A gene (coding for p16) is also tested. Relatives of pancreatic cancer patients have an elevated risk of pancreatic cancer themselves. In a study of 570 families where the proband had pancreatic cancer, 7 had multiple first- or second-degree relatives who had had the disease. This suggests that over 1 percent of pancreatic cancer cases occur in high-risk families. Consensus recommendations for secondary screening of high-risk groups were proposed at the Fourth International Symposium on Inherited Diseases of the Pancreas. It was concluded that secondary screening should only be carried out on a research basis and only in patients with HP, individuals from Peutz-Jeghers (PJS) kindreds or families with a history of pancreatic cancer. In the latter case the family history should include at least two first-degree relatives (or 3 more distant relatives), unless the participant requesting screening has a mutation in either of the BRCA genes or CDKN2A (p16). The causative genetic mutation remains unknown in the majority of families, although BRCA2 has been detected in 19 percent of EUROPAC/FaPaCa familial pancreatic cancer kindreds. Hereditary pancreatitis is consistent with autosomal dominance and in contrast to FPC, most but not all of the responsible mutations have been identified in PRSS1 . Cancer risk to 75 years has been variously calculated as 35 to 54 percent. The risk of a pancreatic cancer in those affected by HP in the EUROPAC population is 4-5 times less than in FPC families. The risks of surgery are ameliorated as any resection would be of diseased pancreatic tissue, with affected individuals likely to already have endocrine and exocrine pancreatic failure. PJS is characterised by autosomal dominant inheritance of hamartomatous polyposis. It is described as conferring a 132-fold increased risk of pancreatic cancer. In many cases those affected by this syndrome have mutations in the STK11 gene, but it is worth noting that mutations in this gene do not appear in FPC kindreds. Familial atypical multiple mole melanoma (FAMMM) is characterised by multiple atypical (dysplastic) naevi and malignant melanoma. An association between FAMMM and pancreatic cancer is well established, but seems to be limited to a subset of families which have been defined on this basis as suffering from FAMMMpancreatic carcinoma syndrome. Mutations in the tumour suppressor CDKN2A are associated with FAMMM and have been described in families with multiple cases of pancreatic cancer but only in families which also have a high incidence of melanoma. Breast ovarian cancer syndrome is often associated with mutations in BRCA2 or BRCA1 genes and BRCA2 is associated with some FPC families. BRCA1 has not been linked to FPC and only confers a slight increase in pancreatic cancer risk (between 1.3- and 4.1-fold increase). However, it cannot be excluded that, in a manner similar to BRCA2, it may confer a much greater risk in the rare families that already include a case of pancreatic cancer. If 100,000 individuals were screened with a modality that had 98 percent specificity there would be 2,000 false positives and only 10 possible lives saved by early detection (even assuming 100 % sensitivity). The pre-test incidence of cancer would have to be at least 2 percent in order for a screening programme with this level of specificity to potentially benefit more people than it harmed. Only the high-risk groups described above offer the possibility of this level of incidence in a reasonable screening

window. Later generations tend to have an earlier onset of cancer; thus maximum risk is at approximately the age of onset in affected siblings and is somewhat lower than the age of onset in affected parents. None of screening programmes in action today assume any significant positive predictive value for any of the blood tests used, but the results may inform clinical decisions based on imaging. EUS meets many of the criteria as the ideal imaging modality in screening, but there are limitations. EUS is not good at distinguishing between benign lesions and cancers. In a small study (n=85) aimed at distinguishing between chronic pancreatitis and pancreatic cancer, positive predictive value was only 60 percent based on imaging alone. Initial results have been published by the Johns Hopkins and Washington groups. From a total cohort of 75 patients, 15 had abnormalities on EUS and ERCP, all of whom had surgery (12 total and 3 distal pancreatectomies). The three that had distal pancreatectomy remain under surveillance. Histology results revealed PanIN-3 lesions in 10 individuals and the remaining 5 specimens contained PanIN-2. Although no cancers were detected in the resected participants, 1 individual has developed an unresectable pancreatic malignancy whilst under imaging surveillance. Screening for early pancreatic cancer remains difficult and has yet to be proven to be effective. The detection of early tumours will not only confirm the validity of the successful screening modality but will reveal more about the early stages of pancreatic cancer development [356].

Lynch syndrome

Lynch syndrome is an inherited cause of colorectal cancer caused by mutations of DNA mismatch repair (MMR) genes. A number of extracolonic tumors have been associated with the disorder, including pancreatic cancer; however, the risk of pancreatic cancer in Lynch syndrome is uncertain and not quantified. To estimate pancreatic cancer risk in families with germline MMR gene mutations cancer histories of probands and their relatives were evaluated in MMR gene mutation carriers in two US familial cancer registries. Families enrolled before the study start date (June 2008) were eligible. Age-specific cumulative risks and hazard ratio estimates of pancreatic cancer risk were calculated and compared with the general population using modified segregation analysis, with correction for ascertainment. Age-specific cumulative risks and hazard ratio estimates of pancreatic cancer risk were calculated. Data on 6342 individuals from 147 families with MMR gene mutations were analyzed. Thirty-one families (21 %) reported at least 1 case of pancreatic cancer. Forty-seven pancreatic cancers were reported (21 men and 26 women), with no gender-related difference in age of diagnosis (52 vs 57 years for men and women, respectively). The cumulative risk of pancreatic cancer in these families with gene mutations was 1.3 percent (95 % confidence interval 0.31 % to 2.32 %) up to age 50 years and 3.7 percent (95 % confidence interval 1.5 % to 5.9 %) up to age 70 years, which represents an 8.6-fold increase (95 % confidence interval 4.7 to 15.7) compared with the general population. It was concluded that among 147 families with germline MMR gene mutations, the risk of pancreatic cancer was increased compared with the US population [357].

Clinical aspects of Lynch syndrome

Hereditary nonpolyposis colorectal cancer, or Lynch syndrome, is responsible for 2-3 percent of all colorectal cancers. Lynch syndrome is also associated with a high risk of extracolonic cancers, including endometrial, stomach, small bowel, pancreas, biliary tract, ovary, urinary tract, brain, and skin cancer. It was now discussed the risks, surveillance tests, and guidelines for the management of extracolonic tumours associated with Lynch syndrome. For all types of extracolonic cancer, evidence supporting surveillance is scarce. A benefit of surveillance is evident only for endometrial cancer, where transvaginal ultrasound and endometrial sampling detect tumours in early stages. Surveillance is generally recommended for urinary tract and gastric cancer, especially in families with more than one member with these types of cancer. For the other types of cancer, surveillance is typically not recommended. Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be

considered for women with Lynch syndrome who are past childbearing age, especially during surgery for colorectal cancer. No data show efficacy of chemopreventive drugs in reducing the risk of extracolonic cancers for patients with Lynch syndrome [358].

Molecular biology

As with many human malignancies, pancreatic cancer is a complex genetic disorder. Several thousand disease-associated alterations on the DNA, mRNA, miRNA and protein levels have been reported to date. Some of these alterations, including a number of gatekeeper mutations, which are of pre-eminent importance for the onset and progression of the disease, have been extensively studied in primary tissues, in vitro experiments and transgenic mouse models. For the vast majority of alterations, however, data about the functional significance are lacking. The situation is complicated by the fact that no certainty exists concerning the identity of the cells that originally undergo malignant transformation nor about the precise nature and fate of premalignant lesions that are observed in pancreatic tissues [359].

Most cases of pancreatic cancer are diagnosed at an advanced stage when the disease is beyond surgical intervention. Molecular studies during the past decade have contributed greatly to our understanding of this disease. Various germ-line and somatic mutations associated with pancreatic cancers have been characterized, along with abnormal variations in the gene expression patterns. A thorough characterization of molecular alterations such as genetic and epigenetic changes, alterations in the expression of genes and changes in proteins, and posttranslational modifications in pancreatic cancer could lead to a better understanding of its pathogenesis. The available data from pancreatic cancer suggests that there are a large number of molecular alterations at genomic, epigenetic, transcriptomic, and proteomic levels. It is now possible to initiate a systems approach to studying pancreatic cancer especially in light of newer initiatives to dissect the pancreatic cancer genome [360].

Methodology

Genomic analysis using tissue samples is an essential approach in cancer genetics. However, technical and biological limits exist in this approach. Microsatellite instability (MSI) is frequently observed in human tumors. MSI assays are now prevalent and regarded as commonplace. However, several technical problems have been left unsolved in the conventional assay technique. Indeed, the reported frequencies of MSI differ widely in each malignancy. An example is pancreatic cancer. Using a unique fluorescent technique, it was found that MSI is extremely infrequent in this malignancy, despite the relatively high frequencies in some reports. In a series of simulations, we have demonstrated that the extremely low frequency was derived neither from less sensitive assays nor from a scarcity of cancer cells in tissue samples. Furthermore, analyzing laser-capture microdissection (LCM)-processed cell populations of a microsatellite-unstable colorectal cancer cell line, HCT116, it was shown that MSI can be detected only when comparing two cell populations that have grown independently to a sufficiently large size. When MSI is not detected in analyses using tissue samples, LCM is not advisable. It was concluded that microsatellite sequence alterations are not detectable in human pancreatic cancer [361].

ACLAM

ALCAM (activated leucocyte cell adhesion molecule, synonym CD166) is a cell adhesion molecule, which belongs to the Ig superfamily. Disruption of the ALCAM-mediated adhesiveness by proteolytic sheddases such as ADAM17 has been suggested to have a relevant impact on tumor invasion. Although the expression of ALCAM is a valuable prognostic and predictive marker in several types of epithelial tumors, its role as a prognostic

marker in pancreatic cancer has not yet been reported. In one study, paraffin-embedded samples of 97 patients with pancreatic cancer undergoing potentially curative resection were immunostained against ALCAM, ADAM17 and CK19. It could be show that in normal pancreatic tissue, ALCAM is predominantly expressed at the cellular membrane, whereas in pancreatic tumor cells, it is mainly localised in the cytoplasm. In addition, univariate and multivariate analyses show that increased expression of ALCAM is an adverse prognostic factor for recurrence-free and overall survival. Overexpression of ADAM17 in pancreatic cancer, however, failed to be a significant prognostic marker and was not coexpressed with ALCAM. The findings support the hypothesis that the disruption of ALCAM-mediated adhesiveness is a relevant step in pancreatic cancer progression. Moreover, ALCAM overexpression is a relevant independent prognostic marker for poor survival and early tumor relapse in pancreatic cancer [362].

Actinin-4

Actinin-4 is an actin-bundling protein that probably has a tumor-promoting potential in several solid tumors. The present study analyzed the expression of actinin-4 in the pancreas, in localized and metastasized pancreatic ductal adenocarcinoma, and the correlation with clinical outcome. Pancreatic ductal adenocarcinoma tissue from 38 patients, 15 lymph node and 10 liver metastases, normal pancreas, and 4 pancreatic cancer cell lines, were examined by immunohistochemistry, and actinin-4 expression was quantified by immunofluorescence analysis. In the normal pancreas, actinin-4 was most prominently expressed in ductal cells. In the cancers, tumor cells exhibited strong but differential cytoplasmic immunoreactivity for actinin-4. A multivariate analysis revealed actinin-4 immunoreactivity, advanced age, and undifferentiated grade as significant prognostic factors associated with worse survival after resection of the pancreatic cancer. Cells metastasized to lymph nodes or to the liver exhibited no significant increase of actinin-4 compared with the primary tumors. A nuclear staining was observed neither in any of the cancer samples nor in the 4 cell lines. In cancer cells, actinin-4 localized to dynamic actin structures and to invadopodia. It was concluded that actinin-4 expression levels significantly correlate with worse survival after resection of pancreatic cancer. Although actinin-4 has been reported to promote lymph node metastases, there was no enhanced expression in cancer metastases [363].

ADAMTS

ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) is a family of proteins characterized by the presence of a metalloproteinase domain linked to a variety of specialized ancillary domains. The ADAMTS9 gene (ADAM metallopeptidase with thrombospondin type 1 motif, 9); has been characterized as a novel tumor suppressor gene in and epigenetically silenced in association with lymph node metastases in nasopharyngeal carcinoma. It was reported high-resolution melting analysis used to detect the methylation levels of ADAMTS9 gene in 100 gastric cancers, 100 colorectal cancers, 70 pancreatic cancers, and an equal number of adjacent normal tissues. The frequency of ADAMTS9 methylation in all three types of cancers was significantly higher than in normal tissues. Consistent with previous reports, expression levels of ADAMTS9 were inversely correlated with methylation levels. There was no significant association between ADAMTS9 methylation status and tumor-node-metastasis staging in all three types of cancers. In summary, application of high-resolution melting analysis to large numbers of clinical samples is a rapid and high-throughput way to investigate the epigenetic status of ADAMTS9. The study was novel in evaluating the prevalence of ADAMTS9 methylation based on a large number of tumor samples and showing that epigenetic regulation of ADAMTS9 was associated with carcinogenesis [364].

Annexin A5

Protein misfolding is a central mechanism for the development of neurodegenerative diseases and type 2 diabetes mellitus. The accumulation of misfolded alpha-synuclein protein inclusions in the Lewy bodies of Parkinson's disease is thought to play a key role in pathogenesis and disease progression. Similarly, the misfolding of the beta-cell hormone human islet amyloid polypeptide (h-IAPP) into toxic oligomers plays a central role in the induction of beta-cell apoptosis in the context of type 2 diabetes. In one study, it was shown that annexin A5 plays a role in interacting with and reducing the toxicity of the amyloidogenic proteins, h-IAPP and alpha-synuclein. It was found that annexin A5 is coexpressed in human beta-cells and that exogenous annexin A5 reduces the level of h-IAPP-induced apoptosis in human islets by approximately 50 protein and in rodent beta-cells by approximately 90 protein. Experiments with transgenic expression of alpha-synuclein in Caenorhabditis elegans show that annexin A5 reduces alpha-synuclein inclusions in vivo. Using thioflavin T fluorescence, electron microscopy, and electron paramagnetic resonance, it was provided evidence that substoichiometric amounts of annexin A5 inhibit h-IAPP and alpha-synuclein misfolding and fibril formation. It was concluded that annexin A5 might act as a molecular safeguard against the formation of toxic amyloid aggregates [365].

Basement membrane proteins

The pathogenesis of pancreatic carcinoma is driven by the tumor cells ability to migrate causing invasion and metastases. The correlation between the aberrant expression of basement membrane proteins and the process of tumor invasion and metastasis has not been fully determined. In one study, the influence of laminin, fibronectin, and collagen type IV on migratory activity of 5 different cell lines has been investigated at the level of a single tumor cell using 3-dimensional time-lapse microscopy. All investigated cell lines have shown a high baseline migration. The addition of laminin, fibronectin, and collagen type IV to collagen type I matrix has significantly increased tumor cell migration. Tumor cell migration was strongly inhibited after treating the tumor cells with anti-beta1 monoclonal antibodies. An abundant and continuous expression of laminin, fibronectin, and collagen type IV was found on the basement membrane of perineurium, which sharply promoted tumor cell invasion. The authors concluded that continuous presentation of the basement membrane proteins by perineurium contributes to the affinity of pancreatic cancer cells for the perineural tumor invasion. Blockade of integrins could represent a possible approach to control the basement membrane-guided tumor spread [366].

BCRA1

Available studies allow to estimate that genetic factors play a role in 5-10 percent of patients with pancreatic cancer. Beside other carcinomas, pancreatic cancer occurs in hereditary neoplastic syndromes associated with gene mutations, including CDKN2A, CHEK2, BRCA2. It has also been suggested that BRCA1 mutation is involved given the fact that BRCA1 mutation carriers are at increased risk for pancreatic cancer. However, a role of this mutation is not fully understood. Eighty-eight pancreatic cancer patients (56 males and 35 females) and 3784 carriers of BRCA1 mutation from 1637 families were enrolled in the study. Almost 65 percent of pancreatic cancer patients were cigarette smokers. Genotyping for constitutive BRCA1 gene mutation was performed in all patients with pancreatic cancer. ASA-PCR and PCR-RFLP methods were used to detect BRCA1 (5382insC, C61G, 4153delA) mutations. The frequency of pancreatic cancer in families of BRCA1 mutation carriers was evaluated. No carriers of BRCA1 mutation were identified in patients with pancreatic cancer. Only in 11 families (0.7 %) with BRCA1 mutation carriers, pancreatic cancer was diagnosed. The results suggest that there is no relationship between BRCA1 mutation and pancreatic cancer development in Polish population [367].

B7 ligand family

B7-H3 is a new member of the B7 ligand family and regulates T-cell responses in various conditions. However, the role of B7-H3 in tumour immunity is largely unknown. The purpose of one study was to evaluate the clinical significance of B7-H3 expression in human pancreatic cancer and the therapeutic potential for cancer immunotherapy. It was investigated B7-H3 expression in 59 patients with pancreatic cancer by immunohistochemistry and real-time PCR. Tumour-related B7-H3 expression was abundant in most human pancreatic cancer tissues and was significantly higher compared with that in non-cancer tissue or normal pancreas. Moreover, its expression was significantly more intense in cases with lymph node metastasis and advanced pathological stage. B7-H3 blockade promoted CD8(+) T-cell infiltration into the tumour and induced a substantial anti-tumour effect on murine pancreatic cancer. In addition, the combination of gemcitabine with B7-H3 blockade showed a synergistic anti-tumour effect without overt toxicity [368].

Ciliogenesis

Primary cilia have been proposed to participate in the modulation of growth factor signaling pathways. In one study, it was determined that ciliogenesis is suppressed in both pancreatic cancer cells and pancreatic intraepithelial neoplasia (PanIN) lesions in human pancreatic ductal adenocarcinoma (PDAC). Primary cilia were absent in these cells even when not actively proliferating. Cilia were also absent from mouse PanIN cells in three different mouse models of PDAC driven by an endogenous oncogenic Kras allele. Inhibition of Kras effector pathways restored ciliogenesis in a mouse pancreatic cancer cell line, raising the possibility that ciliogenesis may be actively repressed by oncogenic Kras. By contrast, normal duct, islet, and centroacinar cells retained primary cilia in both human and mouse pancreata. Thus, arrested ciliogenesis is a cardinal feature of PDAC and its precursor PanIN lesions, does not require ongoing proliferation, and could potentially be targeted pharmacologically [369].

COX-2

Overexpression of cyclooxygenase-2 (COX-2) is implicated in cancer development. One study examined the functional relevance of genetic polymorphisms in the COX-2 promoter and evaluated their associations with susceptibility to pancreatic cancer. Genotypes and haplotypes of COX-2 -765G/C, -1195G/A, and -1290A/G were analyzed in 393 pancreatic cancer patients and 786 controls. The -1195AA or -765GC genotype carriers had a 1.34-fold (95 % confidence intervall 1.12 to 1.60) or 1.63-fold (95 % confidence intervall 1.25 to 2.10) excess risk for developing pancreatic cancer. These two variants showed a cooperative effect in context of haplotype, with the odds ratios for the A(-1195)-C(-765)- containing haplotypes being significantly greater than those for the G(-1195)-G(-765)-containing haplotypes. The -765C allele and smoking displayed a multiplicative joint effect, with an odds ratio of 3.72 (95 % confidence intervall 1.70to 8.14) for heavy smokers carrying the -765GC genotype. Biochemical assays suggest that the -765G→C change creates a binding site for nucleophosmin (NPM) and phosphorylated NPM (p-NPM), which acts as a transcriptional inhibitor. Cigarette smoke remarkably increased COX-2 promoter activity, and this effect was more pronounced for the -765C allele compared with the -765G allele. Cigarette smoke reduced nuclear p-NPM levels, which was reversely associated with COX-2 expression. It was thus found that functional COX-2 polymorphisms are associated with susceptibility to pancreatic cancer and tobacco smoke specifically increases -765C promoter activity, which might be mediated by p-NPM [370].

CTNNB1

To use fluorescence in situ hybridization (FISH) to visualize genetic abnormalities in interphase cell nuclei (interphase FISH) of acinar cell carcinoma, ductal adenocarcinoma, and islet cell carcinoma of the pancreas interphase FISH was used to study paraffin-embedded preparations of tissue obtained from 18 patients listed in the Mayo Clinic Biospecimen Resource for Pancreas Research with a confirmed diagnosis of acinar cell carcinoma, ductal adenocarcinoma, islet cell carcinoma, or pancreas without evidence of neoplasia. FISH probes were used for chromosome loci of APC, BRCA2, CTNNB1, EGFR, ERBB2, CDKN2A, TP53, TYMP, and TYMS. These FISH probes were used with control probes to distinguish among various kinds of chromosome abnormalities of number and structure. FISH abnormalities were observed in 12 (80 %) of 15 patients with pancreatic cancer: 5 of 5 patients with acinar cell carcinoma, 5 of 5 patients with ductal adenocarcinoma, and 2 (40 %) of 5 patients with islet cell carcinoma. All 3 specimens of pancreatic tissue without neoplasia had normal FISH results. Gains of CTNNB1 due to trisomy 3 occurred in each tumor with acinar cell carcinoma but in none of the other tumors in this study. FISH abnormalities of all other cancer genes studied were observed in all forms of pancreatic tumors in this investigation. The authors concluded that FISH abnormalities of CTNNB1 due to trisomy 3 were observed only in acinar cell carcinoma. FISH abnormalities of genes implicated in familial cancer, tumor progression, and the 5-fluorouracil pathway were common but were not associated with specific types of pancreatic cancer [371].

Cytokines

Chemokines and their receptors are involved in tumourigenicity and clinicopathological significance of chemokines receptor expression in pancreatic adenocarcinoma is not fully understood. This study was conducted to determine patients' outcome according to the expressions of CXCR4, CXCR7 and HIF-1alpha after resection of pancreatic cancer. Immunohistochemistry for CXCR4, CXCR7 and HIF-1alpha expressions as well as cell proliferative index (Ki-67) was conducted in 71 resected (R0) cancers and their 48 related lymph nodes using tissue microarray. CXCR4 and CXCR7 expressions were positively correlated to HIF-1alpha suggesting a potential role of HIF-1alpha in CXCR4 and CXCR7 transcription activation. Patients with CXCR4(high) tumour expression had significantly shorter overall survival than those with low expression (median survival: 10 vs 43 months), a higher risk of lymph node metastases and liver recurrence. In multivariate analysis, high CXCR4 expression, lymph node metastases and poorly differentiated tumour are independent negative prognosis factors. In a combining analysis, patients with CXCR4(low)/CXCR7(low) tumour had a significantly shorter disease-free survival and overall survival than patients with a CXCR7(high)/CXCR4(high) tumour. CXCR4 in resected pancreatic cancer may represent a valuable prognostic factor as well as an attractive target for therapeutic purpose [372].

Cytokine polymorphism

Many cytokine polymorphisms have been studied for associations with susceptibility to breast, gastric, liver, lung, prostate, and ovarian cancer without conclusive results. The cytokine network, indeed, is characterized by complex interactions, and the final biological effect of a single genetic variation depends on the balance among different molecular signals. As is well known, Th1/Th2 cytokine unbalanced production might predispose to different pathologies, cancer included. In general, a prolonged type 1 inflammatory response might allow that cells accumulating enough "genetic hits" are promoted to neoplastic transformation. On the other hand, IL-13-producing cells through the IL-13/IL-4 receptor-alpha (R-alpha) pathway might facilitate escape from tumor immunosurveillance. Now it was reported data on the evaluation of the influence of some type 2 and type 1 cytokine genetic

polymorphisms as risk factors for pancreatic cancer. There was no overall association between pancreatic cancer risk and single cytokine SNPs. On the other hand, in evaluating the influence of combined cytokine genotypes it was found that the combined IL-10-1082GA heterozygous and IL-4 Ralpha-1902AA homozygous genotype is underrepresented in the pancreatic cancer subject group. As is well known, the IL-10-1082GA genotype is associated with an intermediate production of this regulatory cytokine, whereas the IL-10-1902AA genotype of the IL-4Ralpha gene is associated with a reduced efficiency in signal transduction when the receptor is engaged by IL-13 or IL-4. These results strongly suggest that a genetic background associated to a mild downregulation of type 1 and type 2 inflammatory signals might be protective against pancreatic cancer [373].

Doxycyclins

Tetracyclines such as doxycycline are reported to possess cytotoxic activity against mammalian tumor cells, but the mechanism of their effects on cell proliferation remains unclear. The antitumor effect of doxycycline was therefore investigated in human pancreatic cancer cell line, PANC-1. It was also investigated the effect of doxycycline on expression of a potent proangiogenic factor, interleukin (IL)-8. In excess of 20 microg/ml, cytotoxic effects of doxycycline were accompanied by G_1-S cell cycle arrest and DNA fragmentation in PANC-1 cells. Doxycycline consistently activated transcription of p53, p21 and Fas/FasL-cascade-related genes, while reducing the expression of Bcl-xL and Mcl-1. Doxycycline (5 microg/ml) below the cytotoxic level suppressed endogenous and paclitaxel-induced IL-8 expression. In the mouse xenograft model, doxycycline treatment was shown to suppress tumor growth by 80 percent. It was thus concluded that doxycycline exerts its antitumor effect by activating proapoptotic genes, inhibiting IL-8 expression, and suppressing antiapoptotic genes [374].

Epidermal growth factor receptor

Novel therapeutic agents targeting the epidermal growth factor receptor (EGFR) have improved outcomes for a subgroup of patients with colorectal, lung, head and neck, and pancreatic cancers. In these tumors, the EGFR activation turns on at least five different signaling pathways (RAS/mitogen-activated protein kinase, phospholipase C, phosphatidylinositol 3-kinase/AKT, signal transducer and activator of transcription, and SRC/FAK pathways), which are intimately interconnected, and frequent mutations involving either the receptor itself or downstream effectors have been found. Up to now, it seems that alterations at the EGFR level have major importance in EGFR tyrosine kinase inhibitor response, whereas modifications of downstream effectors could lead to treatment resistance. Furthermore, the understanding of the mechanism of the EGFR network activation provides new hypotheses on potential new anticancer drugs that may be effektive [375].

Epithelial-mesenchymal transition

Expression of transcription factors that mediate epithelial-mesenchymal transition (EMT), such as Twist and Slug, is correlated with poor prognosis in many tumor types. Selected EMT markers were studied in a series of pancreatic ductal adenocarcinomas and benign pancreatic tissues to determine whether expression levels correlated with diagnosis, histologic grade, or patient outcome. Immunohistochemical stains for Twist, Slug, and N-cadherin were performed using a tissue microarray containing 68 pancreatic cancers and 38 samples of normal pancreas or chronic pancreatitis tissues. Twist and Slug were identified in both the nucleus and cytoplasm of benign pancreatic ductal epithelium, chronic pancreatitis, and pancreatic cancer. Compared with normal ductal epithelium, nuclear levels of Twist are decreased in cancer tissue. None of the other EMT markers showed significant differences in staining indices among the diagnostic groups. There were no correlations between EMT marker expression and histologic grade. Epithelial-mesenchymal transition marker

expression was not associated with N-cadherin expression, patient outcome, or duration of survival. It was concluded that decreased expression of nuclear Twist is observed in malignant pancreatic epithelium. However, use of Twist as a diagnostic marker is precluded because decreased expression is also seen in chronic pancreatitis. None of the markers studied were predictive of patient outcome [376].

Fibrinogen

Although changes of plasma fibrinogen have been documented in limited pancreatic malignant tumors, a relationship between plasma fibrinogen and pancreatic cancer in a large-scale clinical study has not been shown. Therefore, preoperative plasma levels of fibrinogen were retrospectively analyzed in 133 pancreatic cancer and 38 pancreatic benign tumor patients. Plasma fibrinogen in pancreatic cancer patients was significantly higher than those with benign pancreatic tumor. The percentage of hyperfibrinogenemia (>4.20 g/L) in pancreatic cancer was 41 percent, and no positive results were obtained in benign pancreatic disease. Plasma fibrinogen levels were increased in pancreatic cancer with advanced tumor stage. Accompanied with the progression of tumor stage, there was an increase in the percentage of positivity of hyperfibrinogenemia in pancreatic cancer. There were significantly higher levels of plasma fibrinogen in the distant-metastasis group than in the no-distant-metastasis group. Univariate and multivariate analysis revealed that high plasma fibrinogen levels (>4.20 g/L) were positively associated with distant metastasis of pancreatic cancer [377].

Glycogen synthas kinase inhibitor

Recent studies have demonstrated that glycogen synthase kinase 3beta (GSK-3beta) is overexpressed in human colon and pancreatic carcinomas, contributing to cancer cell proliferation and survival. Here, we report the design, synthesis, and biological evaluation of benzofuran-3-yl-(indol-3-yl)maleimides, potent GSK-3beta inhibitors. Some of these compounds show picomolar inhibitory activity toward GSK-3beta and an enhanced selectivity against cyclin-dependent kinase 2 (CDK-2). Selected GSK-3beta inhibitors were tested in the pancreatic cancer cell lines MiaPaCa-2, BXPC-3, and HupT3. It was determined that some of these compounds, namely compounds 5, 6, 11, 20, and 26, demonstrate antiproliferative activity against some or all of the pancreatic cancer cells at low micromolar to nanomolar concentrations. Moreover, it was found that the treatment of pancreatic cancer cells with GSK-3beta inhibitors 5 and 26 resulted in suppression of GSK-3beta activity and a distinct decrease of the X-linked inhibitor of apoptosis (XIAP) expression, leading to significant apoptosis. The present data suggest a possible role for GSK-3beta inhibitors in cancer therapy, in addition to their more prominent applications in CNS disorders [378].

Hedgehog pathway

Aberrant activation of the hedgehog pathway has been observed in multiple human cancers, including pancreatic cancer. For this reason, several small-molecule inhibitors of the pathway have been advanced to clinical trials to evaluate their efficacy in treating various solid cancers. It has also been suggested that pancreatic cancer is a particularly good candidate for experimental treatment with hedgehog inhibitors. In the absence of ligands, such as sonic hedgehog (SHH), the membrane receptor patched (PTCH) blocks the smoothened receptor (SMO), repressing its activity. The binding of the SHH ligand to the PTCH receptor diminishes its inhibitory effects on SMO, allowing signal transduction through the pathway that culminates in activation and nuclear translocation of GLI family zinc finger transcription factors. These transcription factors turn on genes in the nucleus that promote cellular proliferation. Therapeutic blockade of the hedgehog pathway eliminates cancer stem cells, improves outcomes, and may effect a cure when combined with gemcitabine in a direct

xenograft model of pancreatic cancer. With respect to a test of therapeutic effect, it is clear from preclinical studies that hedgehog inhibitors should be examined in combination with gemcitabine, the current standard of care for treatment. It has been suggested that those patients with locally advanced pancreatic cancer are the most likely to benefit from a therapeutic approach that involves inhibition of the hedgehog pathway. This subgroup represents up to 30 percent of patients at the time of diagnosis, and these patient have a type of cancer that is characterized by stroma-rich hypovascular tumors that cannot be resected because of large-vessel involvement [379].

HSP27

A prior study suggested serum heat shock protein 27 (HSP27) as a potential marker for pancreatic carcinoma, but its accuracy in differentiating cancer from chronic pancreatitis was not evaluated. Pretreatment serums from 58 pancreatic carcinoma, 44 chronic pancreatitis, and 102 control subjects were collected. Serum HSP27 and carbohydrate antigen 19-9 (CA19-9) levels were analyzed using an enzyme-linked immunosorbent assay and radioimmunoassay, respectively. Heat shock protein 27 levels were significantly higher in cancer and pancreatitis compared with control, but no significant difference was noted between cancer and pancreatitis. By logistic regression, HSP27 was a significant predictor of differentiation between cancer and control but not between cancer and pancreatitis. At a cutoff of 1650 ng/L, the sensitivity and specificity for differentiating cancer from healthy control were 62 percent and 95 percent, respectively. Receiver operating characteristic analyses showed a significantly greater area under curve for CA19-9 compared with HSP27 in differentiating between cancer and control. It was thus concluded that serum HSP27 is increased in both chronic pancreatitis and pancreatic carcinoma but it should not be recommended as a diagnostic marker for pancreatic carcinoma [380].

HuR

Gemcitabine has been the standard of care for pancreatic cancer for a decade but is only effective in some patients. As a prodrug, gemcitabine is activated by different protein kinases. The deoxycytidine kinase (dCK) is the first step of intracellular activation. TStudies on the Hu antigen R (HuR), a stress response protein, on dCK expression and the correlation between HuR expression levels and pancreatic cancer outcome demonstrates that dCK protein concentration levels were regulated by HuR and that a high cytoplasmic HuR level was associated with a sevenfold decreased risk of mortality after resection of pancreatic adenocarcinoma and gemcitabine therapy [381].

IGF-1 receptor

The insulin-like growth factor 1 receptor (IGF-1R) and its associated signalling system has provoked considerable interest over recent years as a novel therapeutic target in cancer. There are in vitro and in vivo data in the published literature of the following compounds targeting IGF-1R components using specific examples: growth hormone releasing hormone antagonists (e.g. JV-1-38), growth hormone receptor antagonists (e.g. pegvisomant), IGF-1R antibodies (e.g. CP-751,871, AVE1642/EM164, IMC-A12, SCH-717454, BIIB022, AMG 479, MK-0646/h7C10), and IGF-1R tyrosine kinase inhibitors (e.g. BMS-536942, BMS-554417, NVP-AEW541, NVP-ADW742, AG1024, potent quinolinyl-derived imidazo (1,5-a)pyrazine PQIP, picropodophyllin PPP, Nordihydroguaiaretic acid Insm-18/NDGA). Pancreatic cancer is among the tumors that have been tested for response [382].

Integrines

Factors mediating the invasion of pancreatic cancer cells through the extracellular matrix

(ECM) are not fully understood. In this study, sub-populations of the human pancreatic cancer cell line, MiaPaCa-2 were established which displayed differences in invasion, adhesion, anoikis, anchorage-independent growth and integrin expression. The results suggest that altered expression of integrins interacting with different extracellular matrixes may play a significant role in suppressing the aggressive invasive phenotype. Analysis of these clonal populations of MiaPaCa-2 provides a model for investigations into the invasive properties of pancreatic carcinoma [383].

Interleukin-13 receptor

Whereas interleukin-13 receptor alpha2 chain (IL-13Ralpha2) is overexpressed in a variety of human solid cancers including pancreatic cancer, it was investigated its significance in cancer invasion and metastasis. It was used two pancreatic cancer cell lines, IL-13Ralpha2-negative HPAF-II and IL-13Ralpha2-positive HS766T, and generated IL-13Ralpha2 stably transfected HPAF-II as well as IL-13Ralpha2 RNA interference knocked-down HS766T cells. Ability of invasion and signal transduction was compared between IL-13Ralpha2-negative and IL-13Ralpha2-positive cells and tumor metastasis was assessed in murine model for human pancreatic cancer with orthotopic implantation of tumors. IL-13 treatment enhanced cell invasion in IL-13Ralpha2-positive cancer cell lines but not in IL-13Ralpha2-negative cell lines. Furthermore, gene transfer of IL-13Ralpha2 in negative cell lines enhanced invasion, whereas its silencing downmodulated invasion of pancreatic cell lines in a Matrigel invasion assay. In vivo study revealed that IL-13Ralpha2-positive cancer metastasized to lymph nodes, liver, and peritoneum at a significantly higher rate compared with IL-13Ralpha2-negative tumors. The expression of IL-13Ralpha2 in metastatic lesions was found to be increased compared with primary tumors, and mice with IL-13Ralpha2-positive cancer displayed cachexia and poor prognosis. Invasion and metastasis also correlated with increased matrix metalloproteinase protease activity in these cells. Mechanistically, IL-13 activated extracellular signal-regulated kinase 1/2 and activator protein-1 nuclear factors in IL-13Ralpha2-positive pancreatic cancer cell lines but not in IL-13Ralpha2-negative cell lines. Taken together, the results show for the first time that IL-13 can signal through IL-13Ralpha2 in pancreatic cancer cells and IL-13Ralpha2 may serve as a prognostic biomarker of invasion and metastasis in pancreatic cancer [384].

K-ras

To investigate the cellular origin(s) of pancreatic ductal adenocarcinoma, it was determined the effect of pancreatic cancer-relevant gene mutations in distinct cell types of the adult pancreas. It was shown that a subpopulation of Pdx1-expressing cells is susceptible to oncogenic K-Ras-induced transformation without tissue injury, whereas insulin-expressing endocrine cells are completely refractory to transformation under these conditions. However, chronic pancreatic injury can alter their endocrine fate and allow them to serve as the cell of origin for exocrine neoplasia. These results suggest that one mechanism by which inflammation and/or tissue damage can promote neoplasia is by altering the fate of differentiated cells that are normally refractory to oncogenic stimulation [385].

KRAS is mutated in more than 90 percent of pancreatic cancer patients, and oncogenic KRAS contributes to pancreatic cancer tumorigenesis and progression. In one report, using an oncogenic KRASV12-based pancreatic cancer cell model, it was developed a chemical genetic screen to identify small chemical inhibitors that selectively target pancreatic cancer cells with gain-of-function KRAS mutation. After screening ~3,200 compounds, it was identified one compound that showed selective synthetic lethality against the KRASV12 transformed human pancreatic ductal epithelial cell over its isogenic parental cell line. These selective KRASV12-synthetic lethal compounds may serve as leads for subsequent development of clinically-effective treatments for pancreatic cancer [386].

Matriptase

Matriptase, also known as MT-SP1, is a type II transmembrane serine protease strongly implicated in both the development and progression of a variety of epithelial cancers. Evidence comes from studies of its expression in human cancers and from mouse models of spontaneous cancer. Matriptase is considered to be a major activator of two key stimulators of invasive growth, namely hepatocyte growth factor/scatter factor and urokinase-type plasminogen activator. The aim of one study was to examine the role of matriptase in pancreatic ductal adenocarcinoma by expression analysis and functional assays in vitro. Immunohistochemical analysis of matriptase performed on microtissue arrays and large samples of 55 pancreatic ductal adenocarcinomas and on 31 samples of normal pancreatic ducts revealed that although matriptase expression differed greatly in both malignant and normal ductal pancreatic tissue, matriptase scores were significantly elevated in pancreatic ductal adenocarcinoma compared to normal pancreatic ducts. To evaluate the role of matriptase during development of pancreatic cancer, we studied the effects of newly designed matriptase inhibitors on the processing of the zymogen of urokinase-type plasminogen activator in the human adenocarcinoma cell lines AsPC-1 and BxPC-3. In both cell lines, at 1 microM, all matriptase inhibitors completely prevented zymogen activation. At lower inhibitor concentrations, the degree of inhibition of zymogen processing correlated with the affinities of the inhibitors towards matriptase indicating that this is a specific result of matriptase inhibition. Furthermore, matriptase inhibitors reduced the phosphorylation of the HGF receptor/cMet and the overall cellular invasiveness of the human pancreatic adenocarcinoma cell line AsPC-1. The findings demonstrate for the first time that matriptase may be involved in the progression of pancreatic ductal adenocarcinoma and that matriptase inhibition may contribute to preventing the progression of this disease [387].

Mitochondrial DNA

The majority of cancer cells harbor homoplasmic somatic mutations in the mitochondrial genome. It was now shown that mutations in mitochondrial DNA (mtDNA) are responsible for anticancer drug tolerance. It was constructed several trans-mitochondrial hybrids (cybrids) with mtDNA derived from human pancreas cancer cell lines CFPAC-1 and CAPAN-2 as well as from healthy individuals. These cybrids contained the different mitochondrial genomes with the common nuclear background. It was compared the mutant and wild-type cybrids for resistance against an apoptosis-inducing reagent and anticancer drugs by exposing the cybrids to staurosporine, 5-fluorouracil, and cisplatin in vitro, and found that all mutant cybrids were more resistant to the apoptosis-inducing and anticancer drugs than wild-type cybrids. Next, it was transplanted mutant and wild-type cybrids into nude mice to generate tumors. Tumors derived from mutant cybrids were more resistant than those from wild-type cybrids in suppressing tumor growth and inducing massive apoptosis when 5-fluorouracil and cisplatin were administered. To confirm the tolerance of mutant cybrids to anticancer drugs, it was transplanted a mixture of mutant and wild-type cybrids at a 1:1 ratio into nude mice and examined the effect by the drugs on the drift of the ratio of mutant and wild-type mtDNA. The mutant mtDNA showed better survival, indicating that mutant cybrids were more resistant to the anticancer drugs [388].

NF-kappaB

Transcription factor nuclear factor-kappaB (NF-kappaB) is constitutively activated in most pancreatic cancer tissues and cell lines but not in normal pancreas nor in immortalized or nontumorigenic human pancreatic ductal epithelial cells. Inhibition of constitutive NF-kappaB activation in pancreatic cancer cell lines suppresses tumorigenesis and tumor metastasis. Recently, we identified autocrine secretion of proinflammatory cytokine interleukin (IL)-1alpha as the mechanism of constitutive NF-kappaB activation in metastatic pancreatic cancer cell

lines. However, the role of IL-1alpha in determining the metastatic potential of pancreatic tumor remains to be further investigated. In one study, it was stably expressed IL-1alpha in the nonmetastatic, IL-1alpha-negative MiaPaCa-2 cell lines. Our results showed that the secretion of IL-1alpha in MiaPaCa-2 cells constitutively activated NF-kappaB and increased the expression of NF-kappaB downstream genes involved in the different steps of the metastatic cascade, such as urokinase-type plasminogen activator, vascular endothelial growth factor, and IL-8. MiaPaCa-2/IL-1alpha cells showed an enhanced cell invasion in vitro compared with parental MiaPaCa-2 cells and induced liver metastasis in an orthotopic mouse model. The metastatic phenotype induced by IL-1alpha was inhibited by the expression of phosphorylation-defective IkappaB (IkappaB S32, 36A), which blocked NF-kappaB activation. Consistently, silencing the expression of IL-1alpha by short hairpin RNA in the highly metastatic L3.6pl pancreatic cancer cells completely suppressed their metastatic spread. In summary, these findings showed that IL-1alpha plays key roles in pancreatic cancer metastatic behavior through the constitutive activation of NF-kappaB [389].

Osteopontin

Pancreatic ductal adenocarcinoma is a lethal disease with etiological association with cigarette smoking. Nicotine, an important component of cigarettes, exists at high concentrations in the bloodstream of smokers. Osteopontin is a secreted phosphoprotein that confers on cancer cells a migratory phenotype and activates signaling pathways that induce cell survival, proliferation, invasion, and metastasis. Here, it was investigated the potential molecular basis of nicotine's role in pancreatic cancer through studying its effect on osteopontin. Nicotine significantly increased osteopontin mRNA and protein secretion in pancreatic cancer cells through activation of the osteopontin gene promoter. The osteopontin mRNA induction was inhibited by the nicotinic acetylcholine receptor antagonist, mechamylamine. Further, the tyrosine kinase inhibitor genistein inhibited the nicotine-mediated induction of osteopontin, suggesting that mitogen activated protein kinase signaling mechanism is involved. Nicotine activated the phosphorylation of ERK1/2, but not p38 or c-Jun NH2-terminal MAP kinases. Inhibition of ERK1/2 activation reduced the nicotine-induced osteopontin synthesis. Rats exposed to cigarette smoke showed a dose-dependent increase in pancreatic OPN that paralleled the rise of pancreatic and plasma nicotine levels. Analysis of cancer tissue from invasive pancreatic cancer patients, the majority of whom were smokers, showed the presence of significant amounts of osteopontin in the malignant ducts and the surrounding pancreatic acini. The data suggest that nicotine may contribute to pancreatic cancer pathogenesis through upregulation of osteopontin. They provide the first insight into a nicotine-initiated signal transduction pathway that regulates osteopontin as a possible tumorigenic mechanism in pancreatic cancer [390].

p21/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 non-smokers [391].

p53

With the aim of improving early detection of pancreatic carcinoma, it was attempted to make correlations among positive immunohistochemical detection of p53 expression, mutations in the p53 gene, and detailed histologic features of pancreatic carcinoma. Seven cases of invasive pancreatic ductal carcinoma demonstrating p53 overexpression were analyzed. Serial 4- and 20-microm sections from paraffin blocks were used for immunodetection of p53 protein and microdissection, respectively. It was used direct sequencing of polymerase chain reaction at 101 p53-positive and 10 p53-negative sites to sequence exons 5 to 8 of p53 and then analyzed these results in concert with detailed histologic features. Regardless of the degree of p53 overexpression, it was detected p53 point mutations in all p53-positive lesions, including 22 noninvasive sites, 17 invasive areas, and 1 lymph node metastasis. No significant correlations were measured between specific p53 mutations and histologic features. Within individual tumors, the same p53 mutation was generally, but not always, detected in different areas in invasive and noninvasive lesions. The results demonstrate that p53 mutation is an early genetic event affecting a diversity of molecular pathways in pancreatic carcinogenesis and indicates a possibility of early diagnosis of pancreatic carcinoma by detecting a few p53-positive cells obtained from the pancreatic fluid [392].

Pain and nerve growth factor

Perineural invasion is one of the most common routes of invasion in pancreatic cancer and the exact mechanism is still not clear. The aim of one study was to investigate the effect of nerve growth factor (NGF) and tyrosine kinase receptor A (TrkA) on perineural invasion and to clarify the possible mechanism of perineural invasion in pancreatic cancer. Expressions of NGF/TrkA were examined in 51 human primary pancreatic cancer using immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR). Immunohistochemical analysis indicated that the presence and kind of perineural invasion are prognostic parameters. Tumors with high NGF expression exhibited significantly more frequent presence of perineural invasion. NGF expression was significantly correlated with metastasis of lymph nodes and involvement of surgical margins. TrkA expression was significantly correlated with degree of perineural invasion. Negative correlations were found between expression of NGF/TrkA and Ki-67. As shown by RT-PCR, mRNA levels of NGF/TrkA with perineural invasion were significantly higher than that without perineural invasion. It was concluded that in pancreatic cancer, overexpression of NGF may contribute to perineural invasion by prompting the hyperplasia of nerves, restraining the apoptosis of tumor cells and specifically combining NGF and TrkA [393].

PPARG

The Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma (PPARG) gene has been associated with diabetes and several cancers. A pilot study tested for the association between Pro12Ala and pancreatic cancer risk in a high-risk sample of smokers. A nested case-control study was conducted in 83 incident cases of pancreatic cancer and 166 matched controls originally recruited into a cohort chemoprevention study of lung cancer. Associations between Pro12Ala and pancreatic cancer risk were measured using conditional logistic regression. Carriers of the G allele (Ala) of the Pro12Ala variant had a borderline increased relative risk of pancreatic cancer compared with homozygous carriers of the C allele (Pro), with an odds ratio of 1.79 (95 % confidence interval 0.96-3.33). Among subjects

randomized to high-dose vitamin A, the odds ratio was 2.80 versus 1.20 in the placebo group. A haplotype including Pro12Ala was also significantly associated with pancreatic cancer risk in all subjects and in subjects randomized to vitamin A. The analysis presents evidence that PPARG may be associated with pancreatic cancer risk [394].

Plasminogen activator

The serine protease urokinase-type plasminogen activator (uPA) and its receptor (uPAR) are known to be involved in the invasion and metastasis of many solid tumors. In one study, it was analyzed the role of the uPAR/uPA system in both the development and progression of pancreatic cancer in invasive ductal adenocarcinomas of the pancreas and their premalignant precursors (PanIN lesions) in 50 patients with long-term clinical follow-up. It was found overexpression of the uPAR in 48 of 50 invasive carcinomas as well as in a large proportion of high-grade PanIN lesions by immunohistochemistry and in situ hybridization. Fluorescence in situ hybridization analysis showed both high- and low-level amplification of the uPAR gene in approximately 50 percent of cases with strictly identical patterns between invasive cancers and their accompanying precursor lesions. These results suggest that pancreatic cancer may develop from PanIN lesions along an alternative rather than a sequential molecular pathway. The detection of the gene amplification of uPAR was a highly significant, adverse prognostic parameter because it likely renders the tumors more sensitive to uPA and its proproliferative and anti-apoptotic signals. It was concluded that the activation of the uPAR/uPA system is an early event in the development of PDA and that uPAR gene amplifications identify a subgroup of particularly aggressive tumors, making the uPAR/uPA system a critical and highly promising target for therapeutic interventions [395].

REG4

Preoperative chemoradiotherapy is one of the key strategies for the improvement of survival in pancreatic cancer; however, no method to predict the response has yet been established. The aim of one study was to prospectively evaluate the predictive value of REG4, a new member of the regenerating (REG) islet-derived family of proteins. Stably REG4-expressing cells were established from a pancreatic cancer cell line and exposed in vitro to gamma-ray or gemcitabine to investigate the relevance of REG4 to the resistance to chemotherapy or radiotherapy. In 23 patients with resectable pancreatic cancer, the serum concentration of REG4 was measured before preoperative chemoradiotherapy, and the histologic response was evaluated after the surgery. A 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay and fluorescence activated cell scanning (FACS) revealed that REG4-overexpressing cells were resistant to [gamma]-radiation but showed a modest resistance to gemcitabine. The patients with a higher REG4 level, but not carcinoembryonic antigen or CA-19-9, showed an unfavorable histologic response to chemoradiotherapy. The patients showing a higher REG4 level experienced local recurrence postoperatively [396].

Rosiglitazone

Evaluate the effect of fenofibrate, bezafibrate, and rosiglitazone on nonalcoholic fatty pancreatic disease and islet peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and PPAR-beta immunostain in mice fed high-fat high-sucrose (HFHS) diet. Two-month-old male mice were fed standard chow (n=10) or HFHS chow (n=40) for 6 weeks. Afterward, HFHS mice were grouped by treatment: untreated HFHS and HFHS treated with rosiglitazone (HFHS-Ro), fenofibrate (HFHS-Fe), or bezafibrate (HFHS-Bz). Medications were administered for 5 weeks. After treatment, the pancreas was removed and analyzed by morphometry, stereology, and immunohistochemistry. Results: The HFHS-fed mice showed altered fasting glucose (+33 %) and insulin (+138 %); increased body (+20 %) and pancreas (+28 %) masses, pancreatic fat (+700 %), islet hypertrophy (+38 %); and decreased GLUT2

immunostain (-60 %). Rosiglitazone reduced fasting glucose and insulin but induced weight gain. Fibrates impeded weight gain, but only bezafibrate prevented islet hypertrophy. The GLUT2 stain was improved in all treatments, and there were no alterations in PPAR-alpha. There were morphological signs of pancreatitis with fenofibrate, although there were no alterations in amylase and lipase. Rosiglitazone exacerbated pancreatic fat infiltration (+75 % vs HFHS group), and bezafibrate increased PPAR-beta expression in pancreatic islets. The authors concluded that rosiglitazone is shown for the first time to exacerbate pancreatic fat infiltration; therefore, precaution has to be taken when rosiglitazone is prescribed to obese patients [397].

Somatostatin receptor subtype 2

The somatostatin receptor subtype 2 (sst2) behaves as a tumor suppressor when expressed and stimulated by its ligand somatostatin in pancreatic cancer. It was reveal a mechanism underlying oncosuppressive action of sst2, whereby this inhibitory receptor upregulates the expression of the secreted angioinhibitory factor thrombospondin-1 (TSP-1), as demonstrated in exocrine BxPC-3 and endocrine BON pancreatic cancer cells. The sst2-dependent upregulation of TSP-1 occurs through the inhibition of the PI3K pathway. It depends on transcriptional and translational events, involving a previously undescribed IRES in the 5'-UTR of TSP-1 mRNA. Chick chorioallantoic membrane was used as an in vivo model to demonstrate that TSP-1 is a critical effector of the inhibitory role of sst2 on the neoangiogenesis and oncogenesis induced by pancreatic cancer cells. TSP-1 reduced in vitro tubulogenesis of endothelial cells when grown in conditioned medium from pancreatic cancer cells expressing sst2, as compared to those expressing the control vector. TSP-1 inhibited tumor cell-induced neoangiogenesis by directly sequestering the proangiogenic factor VEGF, and inactivating the angiogenesis initiated by VEGFR2 phosphorylation in endothelial cells. Using human pancreatic tissue-microarrays, the expression of both sst2 and TSP-1 was shown to be correlated during the pancreatic neoplastic program. Both proteins are nearly undetectable in normal exocrine pancreas and in most invasive cancer lesions, but their expression is strikingly upregulated in most preinvasive cancer-adjacent lesions. The upregulation of both sst2 and TSP-1 tumor suppressors may function as an early negative feedback to restrain pancreatic carcinogenesis [398].

Sphingolipids

Defeating pancreatic cancer resistance to the chemotherapeutic drug gemcitabine remains a challenge to treat this deadly cancer. Targeting the sphingolipid metabolism for improving tumor chemosensitivity has recently emerged as a promising strategy. The fine balance between intracellular levels of the prosurvival sphingosine-1-phosphate (S1P) and the proapoptotic ceramide sphingolipids determines cell fate. Among enzymes that control this metabolism, sphingosine kinase-1 (SphK1), a tumor-associated protein overexpressed in many cancers, favors survival through S1P production, and inhibitors of SphK1 are used in ongoing clinical trials to sensitize epithelial ovarian and prostate cancer cells to various chemotherapeutic drugs. It was reported that the cellular ceramide/S1P ratio is a critical biosensor for predicting pancreatic cancer cell sensitivity to gemcitabine. A low level of the ceramide/S1P ratio, associated with a high SphK1 activity, correlates with a robust intrinsic pancreatic cancer cell chemoresistance toward gemcitabine. Strikingly, increasing the ceramide/S1P ratio, by using pharmacologic (SphK1 inhibitor or ceramide analogue) or small interfering RNA-based approaches to up-regulate intracellular ceramide levels or reduce SphK1 activity, sensitized pancreatic cancer cells to gemcitabine. Conversely, decreasing the ceramide/S1P ratio, by up-regulating SphK1 activity, promoted gemcitabine resistance in these cells [399].

Synuclein-gamma

Perineural invasion is associated with the high incidence of local recurrence and a dismal prognosis in pancreatic cancer. It was previously reported a novel perineural invasion model and distinguished high- and low-perineural invasion groups in pancreatic cancer cell lines. To identify key biological markers involved in perineural invasion, differentially expressed molecules were investigated by proteomics and transcriptomics. Synuclein-gamma emerged as the only up-regulated molecule in high-perineural invasion group by both analyses. The clinical significance and the biological property of synuclein-gamma were examined in 62 resected cases of pancreatic cancer and mouse models. Synuclein-gamma overexpression was observed in 38 (61 %) cases and correlated significantly with major invasive parameters, including perineural invasion and lymph node metastasis. Multivariate analyses revealed synuclein-gamma overexpression as the only independent predictor of diminished overall survival and the strongest negative indicator of disease-free survival. In mouse perineural invasion and orthotopic transplantation models, stable synuclein-gamma suppression by short hairpin RNA significantly reduced the incidence of perineural invasion and liver/lymph node metastasis compared with the control. This study provides in vivo evidence that synuclein-gamma is closely involved in perineural invasion/distant metastasis and is a significant prognostic factor in pancreatic cancer. Synuclein-gamma may serve as a promising molecular target of early diagnosis and anticancer therapy [400].

Tyrosine kinases

The tyrosine kinase (TK) gene family, which encodes important regulators of various signal transduction pathways, is one of the most frequently altered gene families in human cancer. To clarify the somatic mutation profile of TKs in pancreatic cancer, it was performed a systematic screening of mutations in the kinase domains of all human TK genes (636 exons of 90 genes in total) in 11 pancreatic cancer cell lines and 29 microdissected primary tumors. It was identified 15 nonsynonymous alterations that included 9 DNA alterations in cell lines and 6 somatic mutations in primary tumors. In particular, it was identified the previously reported pathogenic mutation of NTRK3 in a KRAS/BRAF wild-type tumor and 2 somatic mutations in the Src family of kinases (YES1 and LYN) that would be expected to cause structural changes [401].

Urokinase-type plasminogen activator

The serine protease urokinase-type plasminogen activator (uPA) and its receptor (uPAR) are known to be involved in the invasion and metastasis of many solid tumors. In one study, it was analyzed the role of the uPAR/uPA system in both the development and progression of pancreatic cancer in invasive ductal adenocarcinomas of the pancreas and their premalignant precursors (PanIN lesions) in 50 patients with long-term clinical follow-up. It was found overexpression of the uPAR in 48 of 50 invasive carcinomas as well as in a large proportion of high-grade PanIN lesions by immunohistochemistry and in situ hybridization. Fluorescence in situ hybridization analysis showed both high- and low-level amplification of the uPAR gene in approximately 50 percent of cases with strictly identical patterns between invasive cancers and their accompanying precursor lesions. These results suggest that pancreatic cancer may develop from PanIN lesions along an alternative rather than a sequential molecular pathway. The detection of the gene amplification of uPAR was a highly significant, adverse prognostic parameter because it likely renders the tumors more sensitive to uPA and its proproliferative and anti-apoptotic signals. It was concluded that the activation of the uPAR/uPA system is an early event in the development of PDA and that uPAR gene amplifications identify a subgroup of particularly aggressive tumors [402].

Pancreatic ductal adenocarcinoma expresses high levels of urokinase-type plasminogen

activator (uPA), its receptor (uPAR) and plasminogen activator inhibitor (PAI)-2, which may play an important role in progression of pancreatic adenocarcinoma. The overexpression of uPAR predicted short survival in PDAC patients. In one study, two different PDAC cell lines were used to examine the effect of small interfering (si) RNAs to uPAR, uPA and PAI-2 on proliferation, apoptosis, migration and MAP kinase activation. In both pancreatic cancer cell lines, siRNA to uPAR significantly inhibited cell proliferation and migration and stimulated apoptosis, to a greater extent than uPA siRNA. When either PDAC cell line was treated with uPAR siRNA, the level of phosphorylated ERK (p-ERK) decreased substantially, whereas phosphorylated p38 (p-p38) increased when compared to non-silencing control, uPA siRNA or PAI-2 siRNA treatment. This resulted in enhancement of the p-p38/p-ERK ratio which favors cancer cell arrest. Interestingly, uPAR protein expression was suppressed by p-ERK inhibition and stimulated with p-p38 inhibition, suggesting the presence of a positive feedback loop between uPAR and ERK. In summary, the data indicate that, of the uPA system, uPAR exerts the strongest effects on pancreatic cancer cells, by acting through the ERK signaling pathway via a positive feedback loop. Disruption of this loop with uPAR siRNA or inhibitor of p-ERK, inhibits PDAC proliferation and migration and promotes apoptosis [403].

Vitamin D

Ecological studies support the hypothesis that there is an association between vitamin D and pancreatic cancer mortality, but observational studies are somewhat conflicting. It was contributed further data to this issue by analyzing the differences in pancreatic cancer mortality across the eastern states of Australia and investigating if there is a role of vitamin D-effective ultraviolet radiation (DUVR), which is related to latitude. Mortality data from 1968 to 2005 were sourced from the Australian General Record of Incidence and Mortality books. Mortality from pancreatic cancer was 10 percent higher in southern states than in Queensland, with those in Victoria recording the highest mortality risk (relative risk, 1.13; 95 % confidence interval, 1.09 to 1.17). It was found a highly significant association between DUVR and pancreatic cancer mortality, with an estimated 1.5 percent decrease in the risk per 10 kJ/m^2 increase in yearly DUVR. These data show an association between latitude, DUVR, and pancreatic cancer mortality. Although this study cannot be used to infer causality, it supports the need for further investigations of a possible role of vitamin D in pancreatic cancer etiology [404].

Proteomics

The purpose of one review was to describe progress in the application of proteomic approaches to advance The understanding of the biology of pancreatic cancer as well as contribute potential protein biomarkers for this disease. It was reviewed proteomic studies relating to pancreatic cancer that have been published in the past 12 months. It was described novel techniques for the simplification of complex protein samples, focusing particularly on emerging methods for reducing the complexity of blood. Both the range of proteomic-based approaches and their sensitivities for the detection of low-abundance proteins has increased. This provides promise that further research will yield insight into pancreatic cancer, including valuable information on proteins that may ultimately serve as biomarkers for pancreatic cancer [405].

Proteomics from lymph node metastases

The aim of one study was to observe different protein profiles in pancreatic cancer with and without lymph node metastasis (LNM), and search for novel LNM-associated proteins, which would help to understand the metastatic mechanisms and provide targets for therapeutic

interventions. Cancer nests were manually miscrodissected from 8 LNM and 7 non-LNM pancreatic cancer tissues, and the protein extracts were then separated by difference gel electrophoresis (DIGE) and identified by MALDI-TOF-TOF. Four differently regulated proteins, ezrin, radixin, moesin, and c14orf166, were selected for further validation by Western blot and immunohistochemistry. In DIGE analysis, it was identified 18 up-regulated proteins and 15 down-regulated proteins in LNM pancreatic cancer nests compared with non-LNM ones. Western blot and immunohistochemical analyses confirmed that radixin, moesin and c14orf166, but not ezrin, had significantly higher expression levels in LNM pancreatic cancers than in non-LNM controls. In conclusion, the specific protein profiles found in this study might provide new insights into the mechanism of lymph node metastasis. For the first time, c14orf166 was identified asa novel metastasis-associated protein, and the roles of radixin, moesin and c14orf166 in cancer metastasis deserve further investigations [406].

Familial pancreatic cancer

Approximately 5-10 percent of individuals with pancreatic cancer report a history of pancreatic cancer in a close family member. In addition, several known genetic syndromes, such as familial breast cancer (BRCA2), the Peutz-Jeghers syndrome, and the familial atypical multiple mole melanoma syndrome, have been shown to be associated with an increased risk of pancreatic cancer. The known genes associated with these conditions can explain only a portion of the clustering of pancreatic cancer in families, and research to identify additional susceptibility genes is ongoing. Even in the absence of predictive genetic testing, the collection of a careful, detailed family history is an important step in the management of all patients with pancreatic cancer. While most pancreatic cancers that arise in patients with a family history are ductal adenocarcinomas, certain subtypes of pancreatic cancer have been associated with familial syndromes. Therefore, the histologic appearance of the pancreatic cancer itself, and/or the presence and appearance of precancerous changes in the pancreas, may increase the clinical index of suspicion for a genetic syndrome [407].

It has been reported that germline mutations in the palladin gene cause the familial aggregation of pancreatic cancer (in Seattle), but the evidence is weak and controversial. It was sequenced the coding regions of palladin gene in 48 individuals with familial pancreatic cancer. It was not found any deleterious mutations and find no evidence to implicate mutations in palladin gene as a cause of familial pancreatic cancer [408].

Histologic precursors

Pancreatic intraepithelial neoplasia (PanIN) is a precursor to invasive ductal adenocarcinoma of the pancreas. Observations made in genetically engineered mouse models suggest that the acinar/centroacinar compartment can give rise to ductal neoplasia. To integrate findings in mice and men, it was examined human acinar cells, acinar-ductal metaplasia (ADM) lesions, and PanINs for KRAS2 gene mutations. Surgically resected pancreata were screened for foci of ADM with or without an associated PanIN lesion. Stromal cells, acinar cells, ADMs, and PanINs were separately isolated using laser capture microdissection. KRAS2 status was analyzed using genomic DNA isolated from the microdissected tissue. Twelve of these 31 foci of ADM occurred in isolation, whereas 19 were in the same lobules as a PanIN lesion. All 31 microdissected foci of acinar cells were KRAS2 gene wild-type, as were all 12 isolated ADM lesions lacking an associated PanIN. KRAS2 gene mutations were present in 14 of 19 (74 %) PanIN lesions and in 12 of the 19 (63 %) foci of ADM associated with these PanINs. All ADM lesions with a KRAS2 gene mutation harbored the identical

KRAS2 gene mutation found in their associated PanIN lesions. Ductal neoplasms of the human pancreas, as defined by KRAS2 gene mutations, do not appear to arise from acinar cells. Isolated AMD lesions are genetically distinct from those associated with PanINs, and the latter may represent retrograde extension of the neoplastic PanIN cells or less likely are precursors to PanIN [409].

Experimental pancreatic cancer

In an effort to provide useful models for preclinical evaluation of new experimental therapeutics, it has been developed orthotopic mouse models of pancreatic cancer. The utility of these models for pre-clinical testing is dependent upon quantitative, noninvasive methods for monitoring in vivo tumor progression in real time. Toward this goal, it was performed whole-body fluorescence imaging and ultrasound imaging to evaluate and to compare these noninvasive imaging modalities for assessing tumor burden and tumor progression in an orthotopic mouse model of pancreatic cancer. Now whole-body fluorescence imaging and ultrasound imaging in the mice both allowed for the visualization and measurement of orthotopic pancreatic tumor implants in vivo. The imaging sessions were well-tolerated by the mice and yielded data which correlated well in the quantitative assessment of tumor burden. Whole-body fluorescence and two-dimensional ultrasound imaging showed a strong correlation for measurement of tumor size over a range of tumor sizes. The findings suggest a complementary role for fluorescence imaging and ultrasound imaging in assessing tumor burden and tumor progression in orthotopic mouse models of human cancer [410].

Early pancreatic cancer

Tumor cell migration along the periphery of blood vessels to remote sites has been termed extravascular migratory metastasis, which is distinct from direct gross tumor infiltration of blood vessels and from intravascular dissemination. A case report was presented where EUS examination was performed with targeted fine-needle aspiration (FNA) of previously unrecognized perivascular cuffing by computed tomography, which established the presence of celiac axis malignant perivascular cuffing in the setting of a T1 pancreatic cancer [411].

Staging

A retrospective study was performed in 87 patients who underwent surgical resection for pancreatic cancer. Preoperative levels of tumor markers such as carbohydrate antigen 19-9 (CA19-9) and duke pancreatic monoclonal antigen type 2 (DUPAN-2) were estimated and analyzed in relation to disease-specific survival (DSS). The CA19-9 level did not correlate with the DUPAN-2 level. Prognosis correlated with CA19-9 levels, and patients with 185 U/mL or lower CA19-9 level showed significantly better disease-specific survival than patients with 186-U/mL or higher CA19-9 level. Patients with 151-800-U/mL DUPAN-2 level showed significantly worse DSS than patients with 801- U/mL or higher DUPAN-2 level, so the prognosis was reversely related to the DUPAN-2 level. Patients with increased levels of both CA19-9 and DUPAN-2 showed significantly worse disease-specific survival than the patients without elevated levels. The independent predictors of poor DSS (hazards ratio, 95 % confidence interval) were the following: non-well-differentiated adenocarcinoma, invasion of the portal vein, and increased levels of both CA19-9 and DUPAN-2 [412].

Recent years have brought important developments in preoperative imaging and use of laparoscopic staging of patients with pancreatic adenocarcinoma. There are few data about

the optimal combination of preoperative studies to accurately identify resectable patients. Therefore, it was conducted a statewide review of all patients with surgically managed pancreatic cancer from 1996 to 2003 using data from the Oregon State Cancer Registry, augmented with clinical information from primary medical record review. It was documented the use of all staging modalities, including CT, endoscopic ultrasonography, and laparoscopy. Primary outcomes included resection with curative intent. The association between staging modalities, clinical features, and resection was measured using a multivariate logistic regression model. There were 298 patients from 24 hospitals who met the eligibility criteria. Patients were staged using a combination of CT (98 %), laparoscopy (29 %), and endoscopic ultrasonography (32 %). The overall proportion of patients who went to surgical exploration and were resected was 87 percent. Of patients undergoing diagnostic laparoscopy, metastatic disease that precluded resection was discovered in 24 (28 %). For patients who underwent diagnostic laparoscopy and were not resected, vascular invasion was the most common determinant of unresectability (57 %). In multivariate analysis, preoperative weight loss and surgeon decision to use laparoscopy predicted unresectability at laparotomy. This population-based study demonstrates that surgeons appear to use laparoscopy in a subset of patients at high risk for metastatic disease. The combination of current staging techniques is associated with a high proportion of resectability for patients taken to surgical exploration. With current imaging modalities, selective application of laparoscopy with a dual-phase CT scan as the cornerstone of staging is a sound clinical approach to evaluate pancreatic cancer patients for potential resectability [413].

Prognostic factors

The purpose of one study was to determine the operative indications for pancreatic cancer with paraaortic lymph node metastases (node 16+). Between 1981 and 2007, 335 patients with pancreatic cancer including 45 node 16) patients underwent extended radical surgery. Although there was no significant difference in survival between the node 16+ patients and the unresectable cases, there were some long-term survivors among the node 16+ patients. Multivariate analysis of the node 16+ patients identified age (59 years or younger), tumor size (>4 cm), and pathologically confirmed portal invasion (pPV+) as independent prognostic factors. The survival of node 16+ patients without these factors was significantly better than the unresectable cases. The survival of patients with only 1 metastatic paraaortic lymph node also was significantly better than the unresectable cases, and tended to be better than those with more than 2 metastatic nodes. It was concluded that node 16 + pancreatic cancer patients with age 60 years or older, tumor size 4 cm or less, and pPV- may benefit from resection [414].

Pancreatic cancer diagnosing and staging

Algorithm

To develop an algorithmic approach to the diagnosis of pancreatic neoplasms that simplifies their pathologic evaluation it was reviewed literature related to the classification of pancreatic neoplasms on the basis of their gross, histologic, and immunohistochemical features. By using a series of dichotomous decisions, the differential diagnosis of a pancreatic neoplasm can be narrowed, and in cases of the more common neoplasms, accurate classification can be achieved [415].

Tumor markers

Aggressive growth and metastases of pancreatic cancer are the result of basement

membrane degradation that may be attributed to the action of matrix metalloproteinase-9 (MMP-9). The aim of one study was to determine the diagnostic and prognostic significance of the measurements of serum MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) in patients with pancreatic cancer. The study involved 78 patients with pancreatic cancer, 45 with chronic pancreatitis, and 70 healthy subjects. It was assayed the serum concentrations of MMP-9, TIMP-1, and classic tumor markers (carbohydrate antigen 19-9 and CEA) and defined the prognostic value and the diagnostic criteria for all the proteins tested. In the patients with pancreatic cancer, the serum levels of MMP-9, TIMP-1, and the tumor markers were higher as compared with those in the patients with chronic pancreatitis and the healthy subjects. The diagnostic sensitivity and the area under the receiver operating characteristic curve for TIMP-1 were higher than for MMP-9 and the tumor markers. The elevated preoperative concentration of MMP-9 was a significant independent prognostic factor for the patients' survival. The authors concluded that the findings indicated a potential clinical significance of serum TIMP-1 and MMP-9 measurements in the diagnosis and prognosis of patients with pancreatic cancer, respectively [416].

Contrast-enhanced ultrasonography

Ultrasound is often the first examination performed in patients with suspicion of pancreatic disease. The introduction of contrast-enhanced ultrasonography (CEUS) has led to great developments in the diagnostic capabilities of ultrasound. Dynamic observation of an enhancement allows a highly sensitive evaluation of any perfusion of the abdominal organs. Study of the pancreas is a new and promising application of CEUS, and can be used to characterize pancreatic lesions visible with conventional ultrasonography (US). One article reviews the clinical and surgical applications of CEUS in different pancreatic diseases and in their management [417].

Contrast-enhanced ultrasound is a relatively new technique, currently used for liver tumors diagnosis. Newer contrast agents are composed of stabilized micro-bubbles capable of traversing the capillary circulation. Lately, the method has also been used in the assessment of pancreatic disorders. Pulse inversion harmonic imaging allows the assessment of the hypervascularised masses as neuroendocrine tumors, of the hypoperfused masses as adenocarcinomas and of the necrotic areas in acute pancreatitis. Also, this imaging method allows a better assessment of the pancreatic tumor resectability and the identification of septa inside the cystic lesion. Contrast-enhanced ultrasound might represent a valuable additional imaging method to contrast CT for selected cases [418].

Endoscopic ultrasonography

The main objective in the management of pancreatic cancer is to perform an early diagnosis and a correct staging of the disease. Endoscopic ultrasonography (EUS) appears to be an essential tool for the diagnosis and staging of pancreatic cancer. EUS diagnostic accuracy for detecting pancreatic tumors ranges from 85 to 100 percent, clearly superior to other imaging techniques. EUS accuracy for the local staging of pancreatic cancer ranges from 70 to 90 percent, superior or equivalent to other imaging modalities. EUS-guided fine-needle aspiration allows a cyto-histological diagnosis in nearly 90 percent of cases, with a very low complication rate. At present, the formal indications for EUS-guided fine-needle aspiration are the necessity of palliative treatment or whenever the possibility of neoadjuvant treatment is present. It could be also indicated to differentiate pancreatic adenocarcinoma from other pancreatic conditions, like lymphoma, metastasis, autoimmune pancreatitis or chronic pancreatitis [419].

Endoscopic ultrasound (EUS) has become well established as a diagnostic modality in gastrointestinal cancer staging. It offers high-resolution imaging and fine-needle biopsy,

which is essential in tumor and nodal staging of gastrointestinal cancers. In the recent decade, however, many therapeutic applications of EUS have become possible. Currently, interventional EUS endoscopy involves celiac plexus neurolysis, pseudocyst drainage, and intratumoral fine-needle injection therapy for inoperable pancreatic malignancy. Emerging techniques include the accurate endoscopic delivery of radioactive beads to localize tumor therapy as well as other therapies, such as radiofrequency ablation or cryotherapy. Diagnostic and therapeutic access to the biliary tree and pancreatic duct is increasingly being used successfully in failed endoscopic retrograde cholangiopancreatography (ERCP) procedures. A review discusses these procedures and several evolving future applications, including vascular access and EUS-guided enteral anastomosis [420].

The role of EUS to evaluate subtle radiographic abnormalities of the pancreas is not well defined. To assess the yield of EUS ± FNA for focal or diffuse pancreatic enlargement/fullness seen on abdominal CT scan in the absence of discrete mass lesions a retrospective database review of 691 pancreatic EUS exams were reviewed. Sixty-nine met inclusion criteria of having been performed for focal enlargement or fullness of the pancreas. Known chronic pancreatitis, pancreatic calcifications, acute pancreatitis, discrete mass on imaging, pancreatic duct dilation (greater than 4 mm) and obstructive jaundice were excluded. FNA was performed in 19/69 (28 %) with 4 new diagnoses of pancreatic adenocarcinoma, one metastatic renal cell carcinoma, one metastatic colon cancer, one chronic pancreatitis and 12 benign results. Eight patients had discrete mass lesions on EUS; two were cystic. All malignant diagnoses had a discrete solid mass on EUS. It was concluded that pancreatic enlargement/fullness is often a benign finding related to anatomic variation, but was related to malignancy in 9 percent of these patients (6/69). EUS should be strongly considered as the next step in the evaluation of patients with focal enlargement of the pancreas when clinical suspicion of malignancy exists [421].

Hyperechogenic pancreas suggestive of fatty replacement is a common finding during endoscopic ultrasound. Recent data have implicated pancreatic steatosis as a risk factor for pancreatitis and pancreatic malignancy. Hepatic steatosis has been linked to obesity, increased age, hypertriglyceridemia, hyperglycemia, and hyperinsulinemia. The objective of one study was to evaluate the effect of body mass index (BMI), hepatic steatosis, and other metabolic risk factors on HP seen on EUS. Patients with hyperechogenic pancreas were identified by a review of a structured EUS database. The degree of echogenicity was judged relative to the liver (or spleen if the liver is hyperechogenic) at a similar depth. Various demographic and metabolic risk factors were assessed. Chronic pancreatitis was excluded based on normal findings on prior imaging studies. Each case was age matched and sex matched to 1 control with a normal pancreas on EUS. By multivariate logistic regression analysis, BMI, hepatic steatosis, and alcohol use in excess of 14 g/wk were highly associated with the presence of hyperechogenic pancreas compared with controls. Hepatic steatosis was the strongest predictor with an odds ratio of nearly 14-fold [422].

Endoscopic ultrasound-guided fine-needle aspiration biopsi

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an effective method for providing tissue diagnosis, but problems occur when lesions are small or the cytological diagnosis is indeterminate. To prospectively evaluate the utility of EUS-FNA in patients with small solid pancreatic lesions and those with initial indeterminate or negative cytological diagnosis a total of 119 EUS-FNA procedures on 46 patients (mean age 56 years) for 47 small solid pancreatic lesions (range 7-30 mm, mean 17 mm in diameter) were studied. FNAs were performed in the presence of a cytopathologist. If cytological diagnoses were indeterminate, EUS-FNA was repeated within 3 weeks. Diagnoses were confirmed histologically or by follow-up (clinical and imaging: EUS ± FNA and CT). On average, 3.7 passes were performed. It was not observed any complications. Initial cytological findings were: malignant 17 (36 %), benign 21 (45 %), and indeterminate 9 (19 %). Eight (78 %) of

the indeterminate findings were confirmed to be malignant on repeated procedures. A diagnosis of pancreatic cancer was subsequently confirmed in 1 patient who had a benign cytological finding. Nineteen patients underwent surgery. Histology confirmed a neoplasm in all cases. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 68, 100, 100, 73 and 83 percent, respectively. After repeated EUS-FNAs of indeterminate findings sensitivity, negative predictive value and diagnostic accuracy rose to 92, 77 and 96 perent, respectively [423].

Patients presenting with suspected pancreatic neoplasm based on a focal pancreatic lesion on computed tomographic (CT) scan/magnetic resonance image (MRI) but without obstructive jaundice were evaluated by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in a retrospective analysis of a prospective database. Patients were excluded if they had obstructive jaundice or the lesion appeared cystic on CT/MRI. In the 213 study patients, a focal pancreatic lesion was identified in 173 patients by EUS. The final diagnosis included adenocarcinoma (n=89), neuroendocrine tumor (n=14), solid pseudopapillary tumor (n=2), metastases (n=4), mucinous cystadenocarcinoma (n=1), benign cyst (n=19), pseudocyst (n=9), abscess (n=4), chronic pancreatitis (n=32), and normal pancreas (n=39). Endoscopic ultrasound-guided FNA had an accuracy of 98 percent for diagnosing malignant neoplasm, with 97 percent sensitivity, 99 percent specificity, 96 percent negative predictive value, and 99 percent positive predictive value. The authors concluded that endoscopic ultrasound-guided FNA is highly accurate for diagnosing malignancy in patients with a focal pancreatic lesion on CT scan/MRI but without obstructive jaundice. Endoscopic ultrasound-guided FNA can potentially be used as a definitive diagnostic test in the management of these patients [424].

It was prospectively evaluated the diagnostic accuracy and major complications of EUS-guided fine needle aspiration (EUS-FNA) in a newly developed EUS program. All procedures were performed by a single endosonographer in the presence of a cytopathologist. Reference standard for classification of final disease included: surgical resection, death from disease progression and repeat radiologic and/or clinical follow-up. Major complications were defined as oversedation, and those that resulted in a physician or emergency department visits, hospitalization, or death. 540 patients (median age 63 years) underwent EUS-FNAs of 656 lesions: lymph nodes (n=248), solid pancreatic masses (n=229), cystic pancreatic masses (n=57), mural lesions (n=41), bile duct/gallbladder (n=28), liver (n= 17), mediastinum/lung (n=17), adrenal (n=15), spleen (n=3) and kidney (n=1). Solid pancreatic masses and bile duct/gallbladder lesions were more likely to have suspicious/atypical cytology when compared to other lesions (9 vs 5 %) and required significantly more passes to achieve a tissue diagnosis. The overall sensitivity, specificity, PPV, NPV and accuracy of EUS-FNA was 92, 97, 98, 88 and 94 percent, respectively. Six patients (1 %) experienced a major complication. One patient died shortly after the procedure due to preexisting pulmonary embolus (0.18 %) [425].

Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) can characterize and diagnose pancreatic lesions as malignant, but cannot definitively rule out the presence of malignancy. To determine the long-term outcome and provide follow-up guidance for patients with negative EUS-FNA diagnosis of suspected pancreatic lesions based on imaging predictors a retrospective review of patients undergoing EUS-FNA for suspected pancreatic lesions, but with negative or nondiagnostic FNA results was conducted. Seventeen of 55 patients (31 %) with negative/nondiagnostic FNA were subsequently diagnosed with pancreatic malignancy. The risk of cancer was significantly higher for patients who had associated lymph nodes on EUS and vascular involvement on EUS. The mean time to diagnosis in the group with falsenegative EUS-FNA diagnosis was 66 days. The true-negative EUS-FNA patients were followed for a mean of 403 days after negative EUS-FNA results without the development of malignancy. It was concluded that for patients undergoing EUS-FNA for a suspected pancreatic lesion, a negative or nondiagnostic FNA does not

provide conclusive evidence for the absence of cancer. Patients for whom vascular invasion and lymphadenopathy are detected on EUS are more likely to have a true malignant lesion and should be followed closely. When a patient has been monitored for six months or more with no cancer being diagnosed, there appears to be much less chance that a pancreatic malignancy is present [426].

It was also described an acute hemorrhage with retroperitoneal hematoma after endoscopic ultrasound-guided fine-needle aspiration of an intraductal papillary mucinous neoplasm of the pancreas [427].

Endoscopic ultrasound-guided trucut biopsy

Endoscopic ultrasound-guided trucut biopsy (EUS-TCB) technique has the advantage of obtaining tissue for histological examination rather than for cytology alone. However, the diagnostic yield may depend on factors related to both technical aspects and the lesions sampled. Safety of EUS-TCB is yet to be established in a large number of procedures. The aim of one study was to determine factors predicting a positive diagnostic yield, and safety for EUS-TCB in a large tertiary referral center-based service. All patients were referred for EUS-guided tissue sampling as a part of their diagnostic workup. Linear-array echoendoscope (GF-2000-OL5, KeyMed) with a 19-gauge trucut needle (Quick-Core, Wilson-Cook) was used by two operators to obtain tissue samples. In total, 247 patients (143 men) aged 57-73 (median 66) had EUS-TCB performed. Lesions sampled were in the pancreas (113), esophagogastric wall (34), and extra-pancreatic areas (100) (lymph nodes: 52). The maximum diameter of the lesion/wall thickness ranged from 0.6 to 5.4 cm (median 3). One to five passes were made (median 3) to obtain tissue cores 2-18 mm (median 10) in length. The procedure failed in 6 percent of cases. The overall diagnostic accuracy was 75 percent. The overall complication rate was 2 percent (bronchopneumonia, minor hemoptysis, minor hematemesis, mucosal tear, retropharyngeal abscess) with no procedure-related deaths. Site of lesion (pancreatic vs extra-pancreatic), site of biopsy (stomach vs duodenum vs esophagus), and number of passes ($\leq$2 vs >2) were signifikant predictors of a positive diagnostic yield in univariate analysis. However, only the site of biopsy and number of passes were independent predictors in multinominal logistic regression. It was concluded that the diagnostic yield of EUS-TCB is higher when lesion is approached through the stomach and better when more than two passes were made. In this large series, the complication rate of 2 percent associated with EUS-TCB was similar to that reported with EUS-fine needle aspiration technique [428].

Computed tomography

Fatty infiltration of the pancreas is generally a diffuse process; however, it may be unevenly distributed in the pancreas. Focal fatty infiltration of the pancreas is usually most prominent in the anterior aspect of the head of the pancreas and seen as a region of decreased attenuation on computed tomography and may simulate pancreatic neoplasm. It may be discussed and illustrated the various features of focal fatty infiltration of the pancreas on multidetector row helical computed tomography with multiplanar reformation images and show how this imaging modality helps to differentiate between focal fatty infiltration of the pancreas and actual pancreatic tumors [429].

Fatty infiltration of the pancreas is generally a diffuse process; however, it may be unevenly distributed in the pancreas. Focal fatty infiltration of the pancreas is usually most prominent in the anterior aspect of the head of the pancreas and seen as a region of decreased attenuation on computed tomography and may simulate pancreatic neoplasm. It was discussed and illustrated the various features of focal fatty infiltration of the pancreas on multidetector row helical computed tomography with multiplanar reformation images and

show how this imaging modality helps to differentiate between focal fatty infiltration of the pancreas and actual pancreatic tumors [430].

EUS versus CT

To compare the performances of EUS to helical CT in the diagnosis and staging of pancreatic adenocarcinoma 42 consecutive patients (mean age 63 years; 25 men) who had surgical exploration and histologically proved pancreatic cancer were retrospectively included. All the patients underwent with endoscopic ultrasonography (EUS) and helical computed tomography (CT). Data analysis compared helical CT, EUS with the surgical data with or without histological study in diagnosis, staging and resectability of pancreatic cancer. Surgical findings were used as gold standard. For positive diagnosis EUS was more sensitive 100 percent (95 % confidence interval 93 to 100) than helical CT 88 percent (77 to 95). However, helical CT was more specific 89 percent (64 to 98) than EUS 83 percent (58 to 96) for small tumors whose diameter is below 2.5 cm in witch EUS was more sensitive in their detection (100 % vs 83 %). In evaluating venous involvement EUS was significantly more sensitive than helical CT (96 % vs 50 %), while CT was significantly more specific (81 % vs 75 %). Regarding lymph nodes invasion, the two imaging technique had the same sensibility (56 %) with better specificity for helical CT (83 % vs 75 %). The accuracy of EUS in identifying the T and N stages were 80 and 67 percent, respectively, while helical CT have an accuracy of 50 and 71 percent, respectively. EUS and helical CT correctly identified all resectable tumors while EUS was more accurate than helical CT in detecting non resectable tumors 94 percent versus 69 percent. It was concluded that EUS remains superior to helical CT in positive diagnosis of pancreatic adenocarcinoma especially for small tumors and also for the diagnosis of venous invasion and in identifying non resectable tumors. The two techniques have the same accuracy in the detection of lymph node involvement [431].

For evaluation of cytotoxic treatment

Response Evaluation Criteria in Solid Tumors (RECIST) guidelines assume spherical shape of tumors. Morphology of pancreatic adenocarcinoma (PAC) on multidetector row computed tomography was investigated to evaluate the applicability of RECIST guidelines. Study population comprised 16 patients with histologically confirmed localized PAC enrolled in a phase II clinical trial of chemoradiation. Pancreatic adenocarcinomas were segmented on baseline and follow-up multidetector row computed tomography with commercially available software. Tumor volumes (mL), RECIST diameter (mm), volume equivalent sphere diameter (VESD, mm), maximum 3-dimensional diameter (M3DD, mm), and elongation value were obtained. RECIST diameter, VESD and M3DD of the tumors at baseline and follow-up were compared to determine differences. Elongation values were analyzed. Mean volume, RECIST diameter, VESD, M3DD, and elongation for baseline versus follow-up studies were 23.12 mL versus 19.43 mL, 41.86 mm versus 39.35 mm, 33.14 mm versus 32.1 mm, 51.76 mm versus 51.73 mm, and 0.67 versus 0.76, respectively. There was a significant difference at baseline and follow-up between RECIST diameter, VESD, and M3DD. The results suggest that pancreatic cancers are not spherical in shape. Evaluation of PAC treatment response based on RECIST guidelines may not be accurate [432].

A prospective study to determine the value of multidetector CT (MD-CT) in assessing the course of nonresectable pancreatic carcinoma during therapy was performed in 26 patients with nonresectable pancreatic carcinoma underwent MD-CT before and after therapy. The examinations were evaluated with regard to tumor size and vascular invasion using an invasion score (IS) by 2 radiologists independently. Diagnosis was confirmed surgically, by biopsy or clinical course. Sensitivity for the assessment of irresectability was 100 percent. Following therapy, 54 percent of all the tumors were smaller (14/26), 42 percent had increased in volume (11/26), and one tumor remained stable (1/26). The IS (veins) during follow-up changed in 26 patients (portal vein: 5 higher, 4 lower; superior mesenteric vein: 12 higher, 5 lower). The IS (arteries) changed in 13 patients (celiac trunk: 3 higher; hepatic artery: 4 higher, 3 lower; superior mesenteric artery: 2 higher, 1 lower). It was concluded that

MD-CT is suitable for evaluating tumor spread during therapy for nonresectable pancreatic carcinoma. The IS is useful for assessing the impact on the veins and arteries, i.e. degree of change in vessel invasion [433].

After neoadjuvant treatment

To evaluate the effect of neoadjuvant combined chemotherapy and radiation therapy (CCRT) on preoperative accuracy of multidetector computed tomography (CT) for resectability and tumor staging in patients with pancreatic head cancer from 2002 to 2007,38 patients with pancreatic head adenocarcinoma underwent multidetector CT before surgery. Of these, 12 patients received neoadjuvant CCRT. The accuracy in determining resectability was 83 percent (10 of 12) in patients who had received neoadjuvant CCRT and 81 percent (21 of 26) in patients who had not. Of 32 patients who underwent pancreaticoduodenectomy, histopathologic tumor staging was reported for T1 (n=2), T2 (n=1), and T3 (n=9) lesions in patents with neoadjuvant CCRT (n=12), and for T3 in all patients without neoadjuvant CCRT (n=20). T-staging accuracy was 67 percent (eight of 12) with neoadjuvant CCRT and 95 percent (19 of 20) without it, which is a significant difference. This means that neoadjuvant CCRT reduces the accuracy of tumor restaging after treatment of pancreatic head cancer, but this effect is not so great as to affect the determination of resectability [434].

PET-CT

The purpose of one study was to evaluate the diagnostic usefulness of PET/CT for pancreatic malignancy. It was retrospectively analyzed medical records of 115 patients with pathologically diagnosed pancreatic cancer between 2003 to 2008 who underwent abdominal CT and PET/CT examination before histological confirmation. CT and PET/CT images were reviewed in single-blinded status and diagnostic ability on primary pancreatic lesion, regional lymph node metastasis, and distant metastasis was evaluated. Ninety-nine patients (86 %) had malignant diseases including 91 cases of adenocarcinoma, and 16 patients (14 %) benign diseases. Only CA 19-9 value and SUV were significantly different between PET/CT positive and negative groups. Sensitivity, specificity and positive predictive values (PPV) of both modality for pancreatic lesion were same (94 %, 62 %, and 95 %, respectively), and negative predictive values (NPV) were 67 percent on CT and 57 percent on PET/CT. PET/CT correctly diagnosed 8 cases (7 %) of falsely diagnosed pancreatic lesion on CT. Nine cases (16 %) of misdiagnosed lymph node metastasis on CT were correctly diagnosed on PET/CT. But, there was no significant difference in the diagnosis of regional lymph node metastasis. Three out of 29 cases of distant metastasis, except 2 cases of supraclavicular lymph node metastasis, were additionally diagnosed by PET/CT. But, overall sensitivity of distant metastasis was significantly higher in CT (83 % vs 69 %). Although PET/CT provided additional correct diagnoses in many cases, it showed fair diagnostic power for primary pancreatic lesion and lymph node metastasis, and lower sensitivity for distant metastasis. Therefore, PET/CT should be used as an supplementary modality of CT in diagnosing pancreatic malignancy [435].

Magnetic resonance imaging (MRI)

To compare diffusion-weighted imaging (DWI) findings and the apparent diffusion coefficient (ADC) values of pancreatic cancer, mass-forming focal pancreatitis (FP), and the normal pancreas DWI (b = 0 and 600 seconds/mm^2) findings of 14 patients with mass-forming FP proven by histopathology and or clinical follow-up, 10 patients with histopathologically-proven pancreatic cancer, and 14 subjects with normal pancreatic exocrine function and normal imaging findings were retrospectively evaluated. ADC values of the masses, the remaining pancreas, and the normal pancreas were measured. On b = 600 seconds/mm^2 DWI, mass-forming FP was visually indistinguishable from the remaining pancreas whereas pancreatic cancer was hyperintense relative to the remaining pancreas. The mean ADC value of

pancreatic cancer was significantly lower than the remaining pancreas, mass-forming FP and pancreatic gland in the control group. There was no significant difference of ADC values between the mass-forming focal pancreatitis and the remaining pancreas. It was concluded that differences on DWI may help to differentiate pancreatic cancer, mass-forming fokal pancreatitis, and normal pancreas from each other [436].

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 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 [437].

The purpose of one study was to investigate whether, at dynamic MRI of the upper abdominal organs, contrast enhancement with gadoxetic acid, a hepatobiliary contrast agent, is comparable with that achieved with an extracellular contrast agent. Dynamic gadoxetic acid-enhanced MRI of the pancreas, spleen, kidney, liver, and abdominal aorta was performed on 50 patients; dynamic gadobutrol-enhanced MRI was performed on a control group of 50 patients; and the images were compared. Dynamic imaging with a T1-weighted volumetric interpolated breath-hold examination gradient-echo sequence (TR/TE, 3.35/1.35; flip angle, 12 degrees) was performed before and 20 (arterial phase), 55 (portal venous phase), and 90 (hepatic venous phase) seconds after bolus injection of gadoxetic acid (0.25 mmol/mL) or gadobutrol (1.0 mmol/mL). Signal-to-noise ratios and enhancement indexes were calculated for each organ and time. All MR images in both groups were of diagnostic quality. During the early dynamic phases, significantly lower mean enhancement indexes were found in the gadoxetic acid group than in the gadobutrol group in the pancreas, spleen, renal cortex, and liver. In the abdominal aorta, the mean enhancement index was greater after bolus injection of gadoxetic acid. It was concluded that early dynamic MRI of the upper abdominal organs, especially the spleen, pancreas, and kidney, benefits from the higher gadolinium concentration of gadobutrol than in the organ-specific contrast agent gadoxetic acid. Higher protein binding resulting in increased relaxivity of gadoxetic acid compensates for the low gadolinium concentration in the abdominal aorta [438].

Perfusion-weighted magnetic resonance imaging can detect the changes of signal intensity in tumors. It was evaluated the prognostic value of perfusion-weighted MRI in 27 consecutive patients with advanced pancreatic cancer. The American Joint Committee on Cancer (AJCC) stages of patients were as follows (8, stage III; 19, stage IV). Imaging acquisition was continually repeated with echo planar sequence every 2 seconds for 2 minutes after a bolus injection of gadolinium. All cases showed transient decreases signal intensity (SR, 7-56 %). These patients were classified into 2 groups at cutoff median SR of 22 percent. The high SR group significantly correlated with the higher stage and the presence of lymph node metastasis. The high SR group had significantly shorter overall survival [439].

Our current understanding of intrafraction pancreatic tumor motion due to respiration is limited. In one study, it was characterized pancreatic tumor motion and evaluated the application of several radiotherapy motion management strategies. Seventeen patients with unresectable pancreatic cancer were enrolled in a prospective internal review board-

approved study and imaged during shallow free-breathing using cine MRI on a 3T scanner. Tumor borders were agreed on by a radiation oncologist and an abdominal MRI radiologist. Tumor motion and correlation with the potential surrogates of the diaphragm and abdominal wall were assessed. These data were also used to evaluate planning target volume margin construction, respiratory gating, and four-dimensional treatment planning for pancreatic tumors. Tumor borders moved much more than expected. To provide 99 percent geometric coverage, margins of 20 mm inferiorly, 10 mm anteriorly, 7 mm superiorly, and 4 mm posteriorly are required. Tumor position correlated poorly with diaphragm and abdominal wall position, with patient-level Pearson correlation coefficients of -0.18-0.43. Sensitivity and specificity of gating with these surrogates was also poor, at 53-68 percent, with overall error of 35-38 percent, suggesting that the tumor may be underdosed and normal tissues overdosed. Motion of pancreatic tumor borders is highly variable between patients and larger than expected. There is substantial deformation with breathing, and tumor border position does not correlate well with abdominal wall or diaphragmatic position. Current motion management strategies may not account fully for tumor motion and should be used with caution [440].

MRCP

To determine the diagnostic accuracy of combined magnetic resonance cholangio-pancreatography (MRCP) and computed tomography (CT) for preoperative diagnosis of Mirizzi syndrome 52 patients with surgically proven Mirizzi syndrome (n=13) and cholecystitis without evidence for Mirizzi syndrome (n=39) underwent both MRCP using single-shot turbo spin echo and 3-dimensional turbo spin echo sequences and CT. Two blinded observers independently and retrospectively reviewed the combination of MRCP and CT images and CT images alone. The overall sensitivity, specificity, positive and negative predictive values, and accuracy of the combination of MRCP and CT were 96, 94, 84, 99, and 94 percent, respectively. Corresponding values of CT were 42, 99, 93, 84, and 85 percent, respectively. The sensitivity, negative predictive value, and accuracy of combined protocol were significantly higher than those of CT alone. It was concluded that the combination of MRCP and CT is useful for preoperative diagnosis of Mirizzi syndrome [441].

Elastograph

It was investigated the feasibility of using real-time tissue elastography (EG) with transcutaneous ultrasonography (EG-US) for pancreatic diseases. A preliminary study (phase I) and a prospective (phase II) study were conducted. Phase I: subjects were 10 volunteers, 5 with cancer, 2 with endocrine tumor, 5 with chronic pancreatitis, 14 with intraductal papillary-mucinous neoplasm. To determine the characteristic EG images (diagnostic criteria for phase II), B-mode images were compared with EG images and histopathologic findings. Phase II: 53 consecutive patients were enrolled. The visualization rate by EG-US in lesions visualized by B mode was assessed, and the correct diagnosis rate by B mode alone (B diagnosis) or in combination with EG-US was evaluated. Phase I showed normal parenchyma with a homogeneous color. In cancer, EG-US showed a markedly hard area with soft spots inside. Endocrine tumor was uniform and soft comparable to parenchyma. Chronic pancreatitis showed a mixture of various colors. In phase II it was identified 77 percent (41/53) of the lesions and observed 60 percent of the (15/25) of the cancers, 3/3 of the endocrine tumor, and 92 percent (23/25) of the cases of chronic pancreatitis cases on EG-US. The B-diagnosis rates ranged from about 70 to 80 percent. The diagnosis rates of the combination were more than 90 percent of lesions of each type [442].

To evaluate the ability of endoscopic ultrasound elastography to distinguish benign from malignant pancreatic masses and lymph nodes a multicenter study was conducted and included 222 patients who underwent EUS examination with assessment of a pancreatic

mass (n=121) or lymph node (n=101). The classification as benign or malignant, based on the real time elastography pattern, was compared with the classification based on the B-mode EUS images and with the final diagnosis obtained by EUS-guided fine needle aspiration (EUS-FNA) and/or by surgical pathology. An interobserver study was performed. The sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic lesions are 92 and 80 percent, respectively, compared to 92 percent and 69 percent, respectively, for the conventional B-mode images. The sensitivity and specificity of EUS elastography to differentiate benign from malignant lymph nodes was 92 percent and 83 percent, respectively, compared to 79 percent and 50 percent, respectively, for the B-mode images. The kappa coefficient was 0.785 for the pancreatic masses and 0.657 for the lymph nodes. EUS elastography is superior compared to conventional B-mode imaging and appears to be able to distinguish benign from malignant pancreatic masses and lymph nodes with a high sensitivity, specificity and accuracy. It might be reserved as a second line examination to help characterise pancreatic masses after negative EUS-FNA and might increase the yield of EUS-FNA for lymph nodes [443].

Metabolomics

Obesity is a worldwide epidemic and a significant risk factor for pancreatic diseases including pancreatitis and pancreatic cancer; the mechanisms underlying this association are unknown. Metabolomics is a powerful new analytical approach for describing the metabolome (compliment of small molecules) of cells, tissue or biofluids at any given time. The aim was now to analyze pancreatic fat content in lean and congenitally obese mice using both metabolomic analysis and conventional chromatography. The pancreatic fat content of 12 lean (C57BL/6J), 12 obese leptin-deficient (Lep^{ob}) and 12 obese hyperleptinemic (Lep^{db}) mice was evaluated by metabolomic analysis, thin-layer and gas chromatography. Pancreata of congenitally obese mice had significantly more total pancreatic fat, triglycerides and free fatty acids, but significantly less phospholipids and cholesterol than those of lean mice. Metabolomic analysis showed excellent correlation with thin-layer and gas chromatography in measuring total fat, triglycerides and phospholipids. Differences in pancreatic fat content and character may have important implications when considering the local pancreatic proinflammatory milieu in obesity. Metabolomic analysis is a valid, powerful tool with which to further define the mechanisms by which fat impacts pancreatic disease [444].

Optical markers

Pancreatic cancer screening has been hampered by the high rate of complications associated with interrogating the pancreas. The closest non-invasively accessible mucosa available for pancreatic cancer screening is the periampullary duodenal tissue. An earlier report has shown the potential of using optical markers to interrogate this tissue for the presence of pancreatic cancer. In one study, it was reported a larger data set of low-coherence enhanced backscattering (LEBS) and elastic light scattering fingerprinting (ELF) optical markers from the periampullary duodenal mucosa. Optical measurements from biopsy samples were acquired from a total of 203 patients with varying clinical classification including healthy controls, a family history of pancreatic cancer, pancreatitis, mucinous cystic precursor lesions, pancreatic cancer, and other pancreatic malignancies. Evaluation of the performance of an independent testing set for discriminating healthy control patients from pancreatic cancer patients showed a 95 percent sensitivity, 71 percent specificity, and 85 percent area under the receiver operator characteristic (AUROC) curve. Importantly, this performance was uncompromised for detecting potentially curable stages of the disease. Additionally, optical markers in higher risk populations such as family history and pancreatitis had values between those of healthy control and pancreatic cancer patients, thus allowing for future investigations of screening from these high risk groups [445].

Quantum dots

It was reported the successful use of non-cadmium-based quantum dots (QDs) as highly efficient and nontoxic optical probes for imaging live pancreatic cancer cells. Indium phosphide (core)-zinc sulfide (shell), or InP/ZnS, QDs with high quality and bright luminescence were prepared by a hot colloidal synthesis method in nonaqueous media. The surfaces of these QDs were then functionalized with mercaptosuccinic acid to make them highly dispersible in aqueous media. Further bioconjugation with pancreatic cancer specific monoclonal antibodies, such as anticlaudin 4 and antiprostate stem cell antigen (anti-PSCA), to the functionalized InP/ZnS QDs, allowed specific in vitro targeting of pancreatic cancer cell lines (both immortalized and low passage ones). The receptor-mediated delivery of the bioconjugates was further confirmed by the observation of poor in vitro targeting in nonpancreatic cancer based cell lines which are negative for the claudin-4-receptor. These observations suggest the immense potential of InP/ZnS QDs as non-cadmium-based safe and efficient optical imaging nanoprobes in diagnostic imaging, particularly for early detection of cancer [446].

Differential diagnosis

Bronchogenic carcinoma

Hyperamylasemia in patients with bronchogenic carcinoma has been reported rarely. One report described a case of lung adenocarcinoma coexisting with hyperamylasemia in a 67-year-old man. Abdominal computed tomograhy and ultrasonography demonstrated a normal pancreas. A mutational analysis of the EGFR gene indicated an in-frame deletion at exon 19. He underwent treatment with gefitinib. Chest radiography follow-up showed a partial response and the amylase level also decreased to normal [447].

Hydatide cyst

Primary hydatid disease of the pancreas is very rare. It was reported a 33-year-old female who was admitted to the hospital with abdominal discomfort due to the pancreatic mass. A diagnosis of a pancreatic cystic mass was established through abdominal ultrasonography and computed tomography scan. Hydatid disease as well as a cystic neoplasm of the pancreas was both thought in the differential diagnosis. Distal pancreatectomy with splenectomy was performed. The histopathologic evaluation of the specimen revealed a hydatid cyst affecting the tail of the pancreas. Hydatid disease should be considered in the differential diagnosis of all cystic masses of the pancreas, especially in endemic regions [448].

GIST

Diagnosis by endoscopic ultrasound of a large aberrant pancreas mimicking malignant gastrointestinal stromal tumor of the stomach was described in a case report [449].

Chronic pancreatitis

Distinguishing chronic pancreatitis from pancreatic ductal adenocarcinoma (PDAC) is a well-known challenge, at both the clinical and the morphologic level. Findings that are specific to PDAC are the presence of duct structures in perineural and vascular spaces and ("naked") ducts in fatty tissue. However, these findings are only observed in specimens containing extrapancreatic tissue. The features that are suggestive of PDAC in specimens from the pancreas include haphazard distribution of ductlike structures (i.e. loss of a lobular pattern),

markedly irregular ductal contours, ruptured ducts, nuclear enlargement, pleomorphism and hyperchromatism, and mitotic figures. Immunohistologic markers that are helpful are carcinoembryonic antigen, MUC1, p53, and Ki-67/ MIB1. There are a few features that are diagnostic and a number that are suggestive of PDAC. Therefore, a combination of several features may be required to clearly distinguish chronic pancreatitis from invasive PDAC [450].

Pseudotumor

A variety of nonneoplastic conditions may form pancreatic masses that mimic carcinoma. Approximately 5-10 percent of pancreatectomies performed with the clinical diagnosis of pancreatic cancer prove on microscopic evaluation to be pseudotumors. To illustrate the clinical and pathologic characteristics of the 2 most frequent pseudotumoral inflammatory conditions, autoimmune pancreatitis and paraduodenal pancreatitis, and describe the criteria that may be useful in the differential diagnosis versus pancreatic carcinoma recent literature and the authors' experience with the clinical and pathologic characteristics of autoimmune pancreatitis and paraduodenal pancreatitis were reviewed. The knowledge of the clinical, radiologic, and pathologic findings in both autoimmune pancreatitis and paraduodenal pancreatitis is crucial in making the correct preoperative diagnosis. Autoimmune pancreatitis, which occurs in isolated or syndromic forms, is characterized by a distinctive fibroinflammatory process that can either be limited to the pancreas or extend to the biliary tree. Its correct preoperative identification on biopsy material with ancillary immunohistochemical detection of dense immunoglobulin G4-positive plasma cell infiltration is possible and crucial to prevent major surgery and to treat these patients with steroid therapy. Paraduodenal pancreatitis is a special form of chronic pancreatitis that affects young males with a history of alcohol abuse and predominantly involves the duodenal wall in the region of the minor papilla. Pathogenetically, the anatomical and/or functional obstruction of the papilla minor, resulting from an incomplete involution of the intraduodenal dorsal pancreas, associated with alcohol abuse represents the key factor [451].

Special symptoms and signs

Hemosuccus pancreaticus

The major symptoms of cancer of the pancreas, even those of the head, are insidious weight loss, abdominal pains, back pain, anorexia, nausea, vomiting and generalized malaise. Jaundice is present in about 90 percent of the patients with cancer of the head and 10-40 percent of those with cancer of body and tail. Massive haemorrhage is an uncommon presentation. Most causes of gastrointestinal haemorrhage respond to conservative treatment. Haemosuccus pancreaticus is a care cause of gastrointestinal hemorrhage and can prove difficult to diagnose. It was presented two with upper gastrointestinal bleeding. Both patients were found to have pancreatic caranoma with bleding into the pancreatic ducts. I was concluded that haemosuccus pancreaticus may present as one of the early symptoms of carcinoma of the pancreas in young patients in our environment [452].

Venous tromboembolism

Several recent studies have shown that the incidence of venous thromboembolism is highest in patients who present with metastatic cancer, particularly cancers associated with a high one-year mortality rate, such as pancreatic cancer. The incidence rate of VTE is highest in the first few months after the diagnosis of cancer, and it decreases over time thereafter. For most cancers, it is not clear to what extent undergoing major surgery adds to the already high risk of VTE associated with the presence of the cancer. However, patients with glioma

clearly have a very high incidence of VTE soon after they undergo any invasive neurosurgical procedure. Active chemotherapy, the use of erythropoetin agents, and the use of certain anti-cancer therapies such as thalidomide, high-dose steroids, and anti-angiogenic therapy also increase the risk of thrombosis. Similar to patients without cancer, the risk of venous thromboembolism is higher in patients with coexisting chronic medical illnesses. Development of VTE is clearly associated with decreased survival and this effect is greater among patients initially diagnosed with local or regional stage cancer compared to patients with metastatic cancer [453].

Venous thrombosis with and without pulmonary embolism is a frequent complication of malignancies and second among the causes of death in tumor patients. Its incidence is reported to be 10 to 15 percent. Since for methodological reasons, this rate can be assumed to be too low and to disregard asymptomatic venous thrombosis, a combined retrospective and prospective study was performed to examine the actual frequency of venous thrombosis in tumor patients. The histories of 409 patients with different tumors, consecutively enrolled in the order of their altogether 426 inpatient treatments, were checked in retrospect for the frequency of venous thrombosis and pulmonary embolism. Subsequently, 97 tumor inpatients were systematically screened, by means of duplex sonography and/or venography, for venous thromboses in the veins of the pelvis and both legs. In the retrospective analysis, where no systematic screening for thromboses was performed and only symptomatic thrombosis was recorded, venous thrombosis was found in 6.6 percent of all tumor patients, whereas in the prospective examination with systematic duplex sonography and / or venography of all patients, the percentage was 33 percent. In the prospective study, 31 percent of venous thromboses were symptomatic and 69 percent asymptomatic. In 39 percent of the cases in the retrospective analysis and 25 percent in the prospective analysis, venous thrombosis occurred during chemotherapy, surgery or radiation therapy. Venous thrombosis was most often seen in metastasizing tumors and in colorectal carcinoma (40 %), haematological system diseases (29 %), gastric cancer (30 %), bronchial, pancreas and ovarian carcinoma (29 %), and carcinoma of the prostate (17 %). It was concluded that regular screening for thrombosis is indicated even in asymptomatic tumor patients because asymptomatic venous thrombosis is frequent, can lead to pulmonary embolism and has to be treated like symptomatic venous thrombosis. This is particularly true for metastasization during chemotherapy, surgical interventions, or radiation [454].

Cancer is the most important acquired but often overlooked risk factor for the development of venous thromboembolism (VTE). Tumors can express procoagulant proteins, for example, and tumor masses may compromise venous blood flow by extrinsic compression of adjacent vessels. Cancers can also induce the production of inflammatory cytokines that indirectly contribute to the development of hypercoagulability and the risk of thromboembolism. Additional risk factors for VTE experienced by patients with cancer include immobilization, because of cancer or its treatment, and the potential presence of thrombophilic genetic factors. Many common therapeutic modalities also increase VTE risk, including surgery, chemotherapy agents, adjuvant hormonal manipulation, the use of angiogenesis inhibitors, and the presence of central venous access devices. The risk of VTE seems to be greater with certain tumor types, such as cancers of the pancreas, kidney, or brain. The value of extensive screening of patients with the first episode of idiopathic thromboembolism for the presence of an occult malignancy remains debatable at this time. VTE continues to pose a substantial risk to patients with cancer because of a variety of tumor-, host-, and therapy-related factors [455].

Venous thromboembolism (VTE) is a well-recognized and relatively frequent complication of malignancy, whereas tumor thrombosis is a rare complication of solid cancers. The correct diagnosis of tumor thrombosis and its differentiation from VTE can alter patient management and prevent unnecessary long-term anticoagulation treatment. To evaluate the contribution of ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography to the

diagnosis of tumor thrombosis and its differentiation from VTE PET/CT scans from 11 patients with suspected tumor thrombosis were retrospectively evaluated. Suspicion arose from positive PET/CT in eight cases or from findings on contrast-enhanced CT in three patients. Criteria for positivity of PET/CT included increased focal or linear uptake of ^{18}F-FDG in the involved vessel. Findings were categorized as PET/CT positive, or PET/CT negative and compared to contrast-enhanced or ultrasound Doppler, pathology where available, and clinical follow-up. Eight occult tumor thromboses were identified by PET/CT-positive scans. Underlying pathologies included pancreatic, colorectal, renal cell, and head-neck squamous cell carcinoma, as well as lymphoma (4 patients). Three thrombotic lesions on contrast-enhanced CT were PET/ CT negative, due to VTE (2 patients) and leiomyomatosis. Accuracy of PET/CT to differentiate between tumor thrombosis and benign VTE was 100 percent in this small study. It was concluded that contrast-enhanced CT defines the extent of thrombotic lesions, while the functional information from PET/CT characterizes the lesions. It appears that PET/CT may be helpful in the diagnosis of occult tumor thrombosis and its differentiation from venous tromboembolism [456].

Obesity

Clinical and basic studies have shown obesity to be associated with an increased incidence and progression of pancreatic cancer. The precise role that pancreatic fat plays in this process has remained undefined. It was tested the hypothesis that pancreatic steatosis would be associated with increased dissemination and reduced survival in patients with resected pancreatic cancer. A case-control analysis was conducted in patients who had undergone resection for pancreatic adenocarcinoma. Twenty lymph node-positive patients and 20 node-negative patients were matched for age (59 vs 63 years), gender (70 % male vs 60 % male), body mass index (24.5 vs 25.6), medical comorbidities (hypertension, diabetes, hyperlipidemia), tumor size (2.8 vs 2.6 cm), and resection status (R0 80 % vs 85 %). Pancreatic neck margins were reviewed in a blinded fashion by two trained investigators. Pancreatic fat (number of cells/5 high power field) and degree of fibrosis (0 to 4+) were recorded. Node-positive patients had significantly more fat cells in the pancreas compared with node-negative patients. Node-positive patients also demonstrated decreased fibrosis compared with node-negative patients. Mean survival was reduced in node-positive patients (19 $\pm$ 3 vs 31 $\pm$ 5 months). These data show that increased pancreatic fat promotes dissemination and lethality of pancreatic cancer. It was therefore conclude that pancreatic steatosis alters the tumor microenvironment, enhances tumor spread, and contributes to the early demise of patients with pancreatic adenocarcinoma [457].

Between 2000 and 2007, 262 patients underwent pancreatoduodenectomy, of whom 240 had complete data, including body mass index (BMI) for analysis. Data on BMI, preoperative parameters, operative details, and postoperative course were collected. Patients were categorized as obese (BMI $\geq$ 30), overweight (BMI $\geq$ 25 and < 30), or normal weight (BMI < 25). Complications were graded according to previously published scales. Other end points included length of postoperative hospital stay, blood loss, and operative duration. Analyses were performed using univariate and multivariable models. There were 103 (43 %) normal-weight, 71 (30 %) overweight, and 66 (28 %) obese patients. There were 5 perioperative deaths (2.1%), with no differences across BMI categories. A significant difference in median operative duration and blood loss between obese and normal-weight patients was identified (439 vs 363 minutes; 650 vs 500 mL). In addition, median length of stay was significantly longer for BMI (9.5 vs 8 days). Although there were no significant differences in superficial wound infections, obese patients did have an increased rate of serious complications compared with normal-weight patients (24 % vs 14 %). It was concluded that obese patients undergoing pancreatoduodenectomy have a substantially increased blood loss and longer operative time but do not have a substantially increased length of postoperative hospital stay or rate of serious complications. These findings should be considered when assessing

patients for operation and when counseling patients about operative risk, but they do not preclude obese individuals from undergoing definitive pancreatic operations [458].

To examine the influence of obesity, as measured by body mass index (BMI) on clinicopathologic factors and survival after pancreatectomy to treat adenocarcinoma a retrospective review and statistical analysis using prospectively collected data was performed. Two hundred eighty-five consecutive patients with data available for BMI calculation who underwent potentially curative pancreas resection to treat adenocarcinoma from 1999 to 2006. It was identified a subset of obese patients (BMI >35) who were at 12-fold risk of lymph node metastasis compared with nonobese patients (BMI $\leq$ 35). The estimated disease-free and overall survival rates were decreased in the obese patients, and the risk of cancer recurrence and death after pancreatectomy was nearly twice that in nonobese patients. It was concluded that obese patients with a BMI of more than 35 are more likely to have node-positive pancreatic cancer and decreased survival after surgical resection. Data suggest that the negative influence of BMI of more than 35 on cancer-related end points is unrelated to the potential complexity of performing major oncologic surgery in obese patients [459].

Diabetes in pancreatic cancer

In Korea, the prevalence of pancreatic cancer (PC) in general population has been reported as 7 in 100,000. However, that in diabetes mellitus (DM) has not been elucidated yet. One study was designed to estimate the prevalence of PC among diabetes mellitus patients, and characterize and compare the patients with diabetes mellitus with and without PC. 5,082 patients (4,890 diabetes mellitus without PC, 78 PC with diabetes mellitus, and 114 PC without diabetes mellitus) were enrolled during a period of 4 years between 2004 and 2008. The prevalence of PC in diabetes mellitus patients was 1.6 percent and that of diabetes mellitus in PC patients was 41 percent. No significant differences in the clinical characteristics except HbAIc and ALP were observed between PC patients with diabetes mellitus and without diabetes mellitus. Among 78 PC patients with diabetes mellitus, diabetes mellitus was diagnosed in 19 (29 %) and 29 (37 %) patients concomitantly or within 2 years prior to the diagnosis of PC, respectively. Among the cases with recent onset diabetes mellitus (less than 2 years duration), the disease duration of diabetes mellitus before the diagnosis of PC was less than 1 year in 14 patients (18 %) and 1 to 2 years in 15 patients (19 %). Diabetes mellitus patients with PC were found to have significantly higher ALT, total bilirubin, and ALP levels than in diabetes mellitus patients without PC. It was concluded that the prevalence of pancreatic cancer in diabetes mellitus patients was 1.6 percent and was higher than in the general population. Recent onset diabetes mellitus was frequent in PC patients (less than 2 years duration) [460].

Coeliac axis stenosis

Patients with celiac axis stenosis are asymptomatic due to the rich collateral blood supply through superior mesenteric artery. However, ligating and dividing gastroduodenal artery during pancreatoduodenectomy can cause ischemic threat especially to liver, less frequently stomach and spleen, or failure of anastomoses. It was presented a case of 27-year-old female who underwent duodenopancreatectomy for pseudopapillary tumor of the head of pancreas. Celiac axis stenosis was found peroperatively and proven during angiography. Although an attempt of endovascular dilatation of celiac axis was unsuccessful, blood supply to the liver was sufficient and therefore it was not performed any other intervention to improve blood flow to the liver. Postoperative course was uneventful. Celiac axis stenosis can be caused by tumor infiltration or lymphadenopathy in malignant disease, atherosclerosis or compression of the median arcuate ligament. The stenosis can be

managed by endovascular treatment or arterial reconstruction. In conclusion the authors propose a management algorithm to prevent the consequences of celiac axis stenosis [461].

Preoperative biliary drainage

It was examined the effect of selective preoperative biliary drainage (BD) on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. Biliary drainage prior to pancreaticoduodenectomy remains controversial. Proponents argue that it facilitates referral to high-volume tertiary centers, while detractors maintain that it increases surgical morbidity and mortality. It was performed a retrospective analysis of single-institution tumor registry database. From 2003 to 2008 90 patients underwent pancreaticoduodenectomy for periampullary mass lesions. Clinicopathologic data were reviewed and analyzed among patients who did and did not receive biliary drainage for their association with perioperative outcomes. Fifty-six patients (62 %) underwent BD, and 34 (38 %) did not. Intraoperative bile cultures were positive for 1 or more species of microorganisms in 88 percent of stented patients (35 of 40). There were no significant differences in fluid requirements, transfusion requirements, or surgery duration between patients who did and did not undergo biliary drainage. Estimated blood loss was significantly increased in patients who received biliary drainage (625 mL vs 525 mL in patients who did not undergo BD), while reoperation was significantly more common in nonstented patients (4 % vs 15 % in patients who did not undergo BD). Intensive care unit stay, overall length of stay, pancreatic leak/abscess/fistula, infectious complications, postoperative percutaneous drainage, hospital readmission, and 30- and 90-day mortality were not significantly different between the two groups. Although preoperative biliary stents may complicate the intraoperative management and lessen the postoperative complications of patients undergoing pancreatic resection, only estimated blood loss and reoperation were significantly different in this cohort. Currently, selective preoperative BD appears appropriate in the multidisciplinary management of patients with periampullary lesions [462].

In one study it was evaluated whether preoperative biliary drainage should be routinely performed in patients with jaundice. The 342 patients undergoing pancreaticoduodenectomy between 2004 and 2008 were analyzed. Of these patients, 303 without biliary drainage were divided into 4 groups: (1) no jaundice, (2) mild jaundice, (3) moderate jaundice, and (4) severe jaundice. Postoperative complications were stratified by severity according to the modified Clavien classification. It was found that patients with jaundice had a higher incidence in subsequent complications than those with no jaundice. The complications were stratified by severity. Compared with those in group 1, patients in groups 2, 3, and 4 had significantly more complications just in grade 2 (16 %, 23 %, 28 %, and 40 %, respectively), but not other more severe grades including 3a, 3b, 4a, 4b, and 5; all of the complications in this grade could be conservatively treated and cured without requiring surgical, endoscopic, or radiological intervention. The incidences of infection and overall complications were higher in patients with drainage than those without, but neither difference was statistically significant. Preoperative drainage should not routinely be performed in patients with jaundice scheduled for pancreaticoduodenectomy, and immediate surgery is preferable [463].

Experimental

One work presented a novel approach to producing manganese (Mn)-doped quantum dots (Mnd-QDs) emitting in the near-infrared (NIR). Surface functionalization of Mnd-QDs with lysine makes them stably disperse in aqueous media and able to conjugate with targeting molecules. The nanoparticles were structurally and compositionally characterized and maintained a high photoluminescence quantum yield and displayed paramagnetism in water. The receptor-mediated delivery of bioconjugated Mnd-QDs into pancreatic cancer cells was

demonstrated using the confocal microscopy technique. Cytotoxicity of Mnd-QDs on live cells has been evaluated. The NIR-emitting characteristic of the QDs has been exploited to acquire whole animal body imaging with high contrast signals. In addition, histological and blood analysis of mice have revealed that no long-term toxic effects arise from MnD-QDs. These studies suggest multimodal Mnd-QDs have the potentials as probes for early pancreatic cancer imaging and detection [464].

To determine the clinical utility of nuclear morphometry by confocal laser scanning microscopy for the diagnosis of malignant biliary strictures 51 patients with bile duct strictures who underwent ERCP were studied. Based on the initial workup, 6 patients were diagnosed with benign strictures, and 12 patients had malignant strictures, while in the remaining 33 cases the diagnoses were inconsistent, due mainly to inadequate samples. Smears from ERCP brushings were stained for DNA with propidium iodide. Nuclear morphometry was assessed on images acquired by a confocal laser scanning microscope. Three parameters-nuclear volume, nuclear shape and nuclear staining intensity-were calculated. Based on these features, a distinctive nuclear morphometric pattern was attributed to the malignant nuclei, and its predictive value was assessed prospectively in the 33 undiagnosed cases. After an overall median follow-up period of 8 months, 19 patients were diagnosed with malignant strictures, and 14 patients were considered to have benign strictures. With respect to the prediction of malignancy, the sensitivity of the described method was 78 percent, the specificity was 63 percent, the positive predictive value was 64 percent, and the negative predictive value was 80 percent. Nuclear morphometry may provide significant information for the diagnosis of malignant bile duct strictures when conventional cytology fails to [465].

Pancreatic cancer cachexia

Cachexia is a devastating process especially in pancreatic cancer patients and contributes to their poor survival. It was attempted to clarify the pathological and molecular changes that occur in the liver during the development of cachexia. Using immunohistochemistry it was investigated the infiltration of inflammatory mononuclear cells in liver biopsies of pancreatic cancer patients with or without cachexia, and the potential relevance of the cells for the nutritional and inflammatory status. Additionally, these findings were compared with the patients' clinical parameters. It was found a significantly higher amount of CD68 immunoreactive macrophages in liver cross sections of patients with pancreatic cancer and cachexia. The number of CD68-positive macrophages was significantly inversely correlated with the nutritional status. Additionally, in these CD68-positive areas a significant increase in IL-6 and IL-1 immunoreactive cells was localized. Moreover, it was found significantly increased areas of CD68-positive macrophages in liver biopsies of patients with a more dedifferentiated (aggressive) grading of the tumor. In conclusion, these results suggest that a crucial interaction between the tumor, PBMCs, and the liver may play a central role in the development and regulation of cachexia. Furthermore, pancreatic cancer may be able to alter systemic organ function even without obvious metastatic disease [466].

Ghrelin is a growth hormone-releasing acylated peptide found to be an appetite stimulant and low levels of it are detected in cachexia. The aim of one study was to investigate the plasma ghrelin levels in cancer patients with a low performance status and weight loss and compare them with those of healthy individuals without weight loss. Thirty patients (median age 65 years) with different malignancies, mainly pancreatic and gastric, and 27 healthy individuals (median age 62 years) were examined. The gender of both groups was well balanced. Plasma ghrelin was measured by a radioimmunoassay kit that uses a polyclonal antibody which recognizes the C-terminal of ghrelin. There was a statistically significant difference in the plasma ghrelin levels of the patients versus the controls, with the patients having much lower levels. The notable reduction of ghrelin levels might be due to the severity

and progression of the disease [467].

Effect of age on outcome

Both morbidity and mortality rates following pancreatic resection increase with advanced age. The reported mortality rates following pancreatic surgery arc underestimated in single-institution studies. There is a significant publication bias where only centers with good results report their outcomes. The population-based data are critical to provide a more realistic view of mortality rates following pancreatic resection. It is essential in counseling elderly patients that they understand that mortality rates are increased, morbidity rates are increased, and the effect of complications often leads to a prolonged convalescence. They will have a longer length of stay and up to a 30 to 40 percent chance that they will not be able to go home but will need to recover in an extended care facility following hospital discharge. Although the morbidity and mortality rates are increased for elderly patients, they are well within the acceptable range for major abdominal surgery when performed at experienced centers. Patients also need to be aware that surgical resection is the only curative option for pancreatic cancer. In reasonable risk elderly patients the benefit of surgical resection does not decrease with age and these patients can experience long-term survival and good quality of life. Once patients over 80 get beyond the 2-year survival mark without cancer recurrence their survival parallels that of their age-matched counterparts. One should also keep in mind that the reported survival rates are mostly for pancreatic cancer, but patients with other periampullary cancers have improved long-term survival when compared with those with pancreatic cancer. Elderly patients also need to be aware of the fact that hospital volume and surgeon experience significantly impact outcomes. The mortality rates following surgery in the oldest patients, those over 80, are nearly twice as high at low-volume facilities compared with high-volume facilities. The overall mortality rate and the difference decrease with decreasing age. This likely represents improved processes of care at experienced centers and better ability to manage the complications of pancreatic surgery, which occur more commonly in elderly patients. It is important to educate both physicians and elderly patients about this difference. Currently, elderly patients are less likely to be resected at high-volume centers than younger patients. The reasons for this are unclear but include lack of awareness of the importance of hospital volume and surgeon experience and reluctance of patients in this age group to travel long distances from home for their care. When reviewing the data, one must be aware that these studies (both population-based and single-institution) are retrospective and subject to significant selection bias. The elderly patients undergoing resection were dearly carefully chosen. There is still nihilism, however, toward aggressive care in these patients, with fewer than 10 percent of patients over 80 with locoregional disease and no comorbidities being resected, whereas 40 percent of patients 66 to 70 in the same category are resected. These data provide an excellent foundation to guide informed decision-making in the elderly population with pancreatic and periampullary cancer. Patients need to know that surgical resection offers the only hope for cure and that the benefit of surgical resection does not diminish with age. The diagnosis (pancreatic versus other periampullary cancers versus benign disease or premalignant lesions) needs to be taken into account to balance fully the risks and benefits. Older patients need to be aware of the increased morbidity, mortality, and prolonged convalescence they may experience. They also need to be advised to have their surgery done by experienced surgeons at experienced centers where these complications can be best managed. Further studies are needed to guide patient selection. The effect of patient comorbidities, cognitive status, preoperative functional status, and frailty need to be more formally assessed to select patients, maximize surgical resection in appropriate candidates, and improve short-term outcomes. Once better characterized, specialized geriatric pathways may optimize surgical resection rates, streamline care, and improve outcomes in this challenging population. Age alone, however, should not be a contraindication to pancreatic resection in elderly patients with pancreatic

cancer [468].

To evaluate pancreatic surgery as a model for high-acuity surgery in elderly patients for immediate and long-term outcomes, predictors of adverse outcomes, and hospital costs. Four hundred twelve consecutive patients who underwent pancreatic resection from 2001, through 2008 for benign and malignant periampullary conditions. Clinical outcomes were compared for elderly (≥ 75 years) and nonelderly patient cohorts. Quality assessment analyses were performed to show the differential impact of complications and resource utilization between the groups. The elderly cohort constituted one-fifth of all patients. Benchmark standards of quality were achieved in this group, including low operative mortality (1 %). Despite higher patient acuity, clinical outcomes were comparable to those of nonelderly patients at a marginal cost increase (median, USD 2202 per case). Cost modeling analysis showed further that minor and moderate complications were more frequent but no more debilitating for elderly patients. Major complications, however, were far more threatening to older patients. In these cases, duration of hospital stay doubled, and invasive interventions were more commonly deployed. It was concluded that quality standards for pancreatic resection in the elderly can – and should – mirror those for younger patients. Age-related care, including geriatric consultation, supplemental enteral nutrition, and early rehabilitation placement planning, can be designed to mitigate the impact of complications in the elderly and guarantee quality [469].

Surgical techniques

Pancreatojejunostomy

To evaluate the impact of the length of the isolated jejunal loop and the type of pancreaticojejunostomy on pancreatic leakage after pancreaticoduodenectomy 132 consecutive patients who underwent a pancreaticoduodenectomy were studied according to the length of the isolated jejunal loop (short loop, 20-25 cm vs long loop, 40-50 cm) and the type of pancreaticojejunostomy (invagination vs duct to mucosa). The use of the long isolated jejunal loop was associated with a significantly lower pancreatic leakage rate compared with the use of a short isolated jejunal loop (4.3 % vs 14.2 %). In addition, the use of duct-to-mucosa technique was associated with significantly lower incidence of postoperative pancreatic fistula compared with the invagination technique (4.2 % vs 14.5 %). Finally, patients with a short isolated jejunal loop compared with patients with a long loop had increased morbidity (50.7 % vs 27.5 %) and prolonged hospital stay (16 ± 2 days vs 10 +/- 2 days). Overall mortality rate was 1.5 percent. It was concluded that the use of a long isolated jejunal loop and a duct-to-mucosa pancreaticojejunostomy is associated with decreased pancreatic leakage rate after pancreaticoduodenectomy [470].

Pancreatic fistula is one of the most common complications after pancreaticoduodenectomy. It was now tested the hypothesis that a duct to mucosa pancreaticojejunostomy would reduce the pancreatic fistula rate. Between 2006 and 2008, 197 patients at two institutions underwent pancreaticoduodenectomy by a total of 8 experienced pancreatic surgeons as part of this prospective randomized trial. All patients were stratified by pancreatic texture and randomized to either an invagination or a duct to mucosa pancreaticojejunal anastomosis. Recorded variables included pancreatic duct diameter, operative time, blood loss, complications, and pathology. Primary end point was fistula rate, as defined by the International Study Group on Pancreatic Fistula. Rate of pancreatic fistula rate for the entire cohort was 18 percent. There were 23 fistulas (24 %) in the duct to mucosa cohort and 12 fistulas (12 %) in the invagination cohort, which was a statistically significant difference. The greatest risk factor for a fistula was pancreas texture: pancreatic fistulas developed in only 8 patients (8 %) with hard glands, and in 27 patients (27 %) with a soft gland. There were two

perioperative deaths (both in the duct to mucosa group), with the proximate causes of death being pancreatic fistula, followed by bleeding and sepsis. This dual-institution prospective randomized trial reveals considerably fewer fistulas with invagination compared with duct to mucosa pancreaticojejunostomy after pancreaticoduodenectomy [471].

To evaluate the impact of the length of the isolated jejunal loop and the type of pancreaticojejunostomy on pancreatic leakage after pancreaticoduodenectomy 132 consecutive patients who underwent a pancreaticoduodenectomy were studied according to the length of the isolated jejunal loop (short loop, 20-25 cm vs long loop, 40-50 cm) and the type of pancreaticojejunostomy (invagination vs duct to mucosa). The use of the long isolated jejunal loop was associated with a significantly lower pancreatic leakage rate compared with the use of a short isolated jejunal loop (4 % vs 14 %). In addition, the use of duct-to-mucosa technique was associated with significantly lower incidence of postoperative pancreatic fistula compared with the invagination technique (4 % vs 15 %). Finally, patients with a short isolated jejunal loop compared with patients with a long loop had increased morbidity (51 % vs 28 %) and prolonged hospital stay (16 + 2 days vs 10 + 2 days). Overall mortality rate was 1.5 percent. It was concluded that the use of a long isolated jejunal loop and a duct-to-mucosa pancreaticojejunostomy is associated with decreased pancreatic leakage rate after pancreaticoduodenectomy [472].

It was compared the different techniques for pancreatojejunostomy using the definitions of the International Study Group of Pancreatic Surgery for postoperative complications after pancreaticoduodenectomy. Perioperative data of 119 patients that underwent pancreatico-duodenectomy by a single surgeon were retrospectively analyzed. Pancreaticojejunal anastomosis was performed using the dunking method (n=39), the duct-to-mucosa anastomosis method (n=40), and the duct-to-mucosa adaptation (n=40). The most frequent complication was postoperative pancreatic fistula (POPF; grades A, 21 %; B, 8 %; and C, 3 %), postpancreatectomy hemorrhage (PPH; grades B, 7 % and C, 1 %), and delayed gastric emptying (DGE; grades A, 1 % and B, 6 %). No significant differences in POPF were found between patients who underwent different types of pancreatic anastomoses. Only pancreatic ductal adenocarcinoma and pancreatic texture were potentially related to fistulas. Patients with or without fistulas grade A had shorter postoperative stays than patients with grade B or C fistulas, and similar findings were obtained for DGE and PPH. It was concluded that the successful management of pancreatic anastomoses depends more on a meticulous surgical technique and appropriate experience rather than on the type of technique. Furthermore, the International Study Group of Pancreatic Surgery definitions of postoperative pancreatic fistula, postpancreatectomy hemorrhage, and delayed gastric emptying seem objective and universally acceptable [473].

Pancreaticoduodenectomy is the standard treatment for periampullary tumors. One of the major causes of morbidity after pancreaticoduodenectomy is the failure of the healing at the pancreaticoenteric anastomosis. The aim of one study is to summarize the results of a new technique which is designed to decrease the panreticoje-junostomy anastomotic leakage. Consecutive patients whose pancreaticojejunostomy anastomosis after pancreatico-duodenectomy was performed by modified invagination method were evaluated prospectively. Thirtyone patients were included in the study. Twenty complications had occurred in a total of 15 patients. There were no pancreaticojejunostomy anastomotic leakage and mortality in any of the patients. An ideal pancreaticojejunostomy anastomosis after pancreaticoduodenectomy should be safe, simple and secure. This modified invagination method seems to be promising when these parameters are taken in to account [474].

The aim of one study was to compare postoperative morphological changes in remnant pancreas between pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) after

pancreaticoduodenectomy (PD). The study subjects were 28 patients with PJ and 14 with PG. The diameter of the main pancreatic duct (MPD) and pancreatic parenchymal thickness 2 years after PD were measured on computed tomography scans and compared between the 2 groups. The preoperative and postoperative MPD diameter was 5.2 mm (SD, 2.4 mm) and 4.2 mm (SD, 2.0 mm) in the PJ group and 4.8 mm (SD, 3.2 mm) and 5.7 mm (SD, 1.8 mm) in the PG group, respectively. In those patients with preoperatively normal-size MPD, MPD after surgery tended to become dilated relative to before surgery in the PJ group, and the MPD measured postoperatively was significantly larger than preoperatively in the PG group. A significant atrophy of the pancreatic parenchyma was noted postoperatively in both groups, but these changes were significantly more severe in the PG group than the PJ group [475].

Bioabsorbable staple line-reinforcement

To investigate the use of Seamguard, a bioabsorbable staple line-reinforcement product, to prevent pancreatic leak after distal pancreatectom a retrospective study examined 85 consecutive patients undergoing distal pancreatectomy at an academic institution from 1997, to 2007. Indications for resection included trauma (11 patients), neoplasms (62 patients), and chronic pancreatitis (12 patients). Pancreatic leak was defined as drain output of 25 mL/d or more 7 days postoperatively with a drain amylase level of 1000 U/L or more. Pancreatic leak occurred in 10 of 38 patients (26 %) undergoing conventional resection with suture ligation of the pancreatic duct or nonreinforced stapled resection versus 2 of 47 patients (4 %) undergoing staple resection using Seamguard reinforcement. Multivariate analysis showed that use of Seamguard with the stapler independently decreased the risk for pancreatic fistula after distal pancreatectomy (odds ratio, 0.07; 95 % confidence interval 0.01 to 0.43). It was concluded that the use of Seamguard is quickly becoming a common adjunct in distal pancreas resections. The study shows a lower incidence of pancreatic leak after distal pancreatectomy with the use of this staple line-reinforcing product [476].

Pancreatic fistula is a major cause of morbidity after distal pancreatic resection. When resections are performed with linear stapling devices, the use of bioabsorbable staple line reinforcement has been suggested to decrease the rate of pancreatic fistula. The objective of one study was to investigate the incidence of pancreatic fistula when using the Gore Seamguard staple line reinforcement in stapled distal pancreatic resections. A retrospective review of 30 consecutive patients with stapled distal pancreatectomy was conducted. A broad definition of pancreatic fistula was used. Clinicopathologic factors and outcomes were compared between groups. Pancreatic fistula was diagnosed in 11 of 15 patients (73 %) and three of 15 patients (20 %) in the Seamguard and non-Seamguard groups, respectively. Pancreatic parenchymal transection at the neck of the gland was associated with pancreatic fistula, whereas laparoscopic procedures, splenic preservation, or additional organ resection were not. On multivariate analysis, the association between Seamguard use and pancreatic fistula was significant. In conclusion, after introduction of the Gore Seamguard bioabsorbable staple line reinforcement, it was experienced a significant increase in the rate of pancreatic fistula. This experience raises concern about the efficacy of this device in limiting pancreatic fistula after stapled distal pancreatic resection [477].

Total pancreatectomy

In one study, it was reappraised the outcomes of total pancreatectomy, retrospectively analyzing the safety of the procedures and factors associated with long-term survival. Thirty-six consecutive patients underwent total pancreatectomy for pancreas disease. Postoperative morbidity was 39 percent (14/36) and severe complications were anastomotic leakage (n=3) and liver necrosis (n=1). In benign disease, 5-year survival was 50 percent, while 5-year survival in malignant disease was 22 percent. Postoperative glycosylated

hemoglobin A1c (HbA1c) level was 7.8 ± 1.2 percent at 6 months and 7.8 ± 1.5 percent at 12 months after total pancreatectomy, respectively. It was concluded that total pancreatectomy can be safely performed and the treatment option for selectively limited pancreatic cancer and intraductal papillary mucinous neoplasm of the pancreas (IPMN), when the patient condition permits and offers a chance of cure, although careful long-term medical care and follow-up are essential [478].

With preserving stomach and spleen

Total pancreatectomy has been used to treat both benign and malignant diseases of the pancreas. The procedure of total pancreatectomy for invasive pancreatic cancer usually includes distal gastrectomy and splenectomy to prevent ischemic changes due to decreased blood supply. In one report, it was introduced a new technique of total pancreatectomy for invasive pancreatic cancer preserving both the whole stomach and spleen. It was tried, initially to perform pylorus-preserving pancreatoduodenectomy (PPPD). Repeated frozen section examination of the pancreatic stumps, however, revealed persistent cancer infiltration to the distal pancreas. Therefore, it was altered the planned PPPD to total pancreatectomy preserving the whole stomach and spleen with severing both the splenic artery and vein at their origins. The postoperative course was uneventful. Enhanced CT following surgery showed sufficient blood supply to the whole stomach and spleen without any congestive changes of blood flow. This method is considered safe and useful for patients with both benign and malignant disease of the pancreas [479].

Portal vein reconstruction

Aggressive preoperative and intraoperative management may improve the resectability rates and outcomes for locally advanced pancreatic adenocarcinoma with venous involvement. The efficacy and use of venous resection and especially arterial resection in the management of pancreatic adenocarcinoma remain, however, controversial. A retrospective review of 2 prospective databases of 593 consecutive pancreatic resections for pancreatic adenocarcinoma from 1999 through 2007 showed that 36 (6 %) underwent vascular resection at the time of pancreatectomy. Thirty-one of the 36 (88 %) underwent venous resection alone; 3 (8 %), combined arterial and venous resection; and 2 (6 %), arterial resection (superior mesenteric artery resection) alone. Patients included 18 men and 18 women, with a median age of 62 (range, 42-82) years. The 90-day perioperative mortality and morbidity rates were 0 and 35 percent, respectively, compared with 2 and 39 percent, respectively, for the group undergoing nonvascular pancreatic resection. Median survival was 18 (range, 8-42) months in the vascular resection group compared with 19 months in the nonvascular resection group. Multivariate analysis demonstrated node-positive disease, tumor location (other than head), and no adjuvant therapy as adverse prognostic variables. This means that in this combined experience, en bloc vascular resection consisting of venous resection alone, arterial resection alone, or combined vascular resection at the time of pancreatectomy for adenocarcinoma did not adversely affect postoperative mortality, morbidity, or overall survival. The need for vascular resection should not be a contraindication to surgical resection in the selected patient [480].

Portal vein-superior mesenteric vein resection is frequently required after surgical resection of tumours of the pancreas head. Between 2000 and 2007, 28 patients had portal vein-superior mesenteric vein resection and PVR during pancreaticoduodenectomy. Their clinical reports were reviewed retrospectively with specific attention to the methods of PVR and outcomes. Ten patients had PVR with primary anastomosis, seven had PVR with autologous vein, one had a polytetrafluoroethylene (PTFE) patch, one did not have PVR and nine had PVR with a PTFE interposition graft. There was no infection after PTFE grafting. Six patients had PVR thrombosis after surgery: four after primary anastomosis, one after interposition PTFE and one after vein repair. It was concluded that PTFE appeared to be an effective and

safe option as an interposition graft for portomesenteric venous reconstruction after pancreaticoduodenectomy [481].

Arterial reconstruction at pancreatic resection

The arterial anatomy supplying the liver is highly variable. A replaced common hepatic artery originating from superior mesenteric artery is a rare anomaly. It was presented the case of a patient with retropancreatic lymph nodes recurrence after laparoscopic cholecystectomy for pT2 gallbladder carcinoma, whose replaced common hepatic artery arose from the superior mesenteric artery. It was performed a Whipple operation en bloc with the replaced common hepatic artery resection (enhanced by the tumour). The arterial reconstruction was needed (due to the severe decrease of the arterial flow after clamping the replaced common hepatic artery), using the splenic artery, without any serious complications [482].

The authors report a case of operative injury of the hepatic artery during a total spleno-pancreasectomy procedure for a mixed-type intraductal papillary mucinous neoplasm. During the preparation of the structures of the hepatic pedicle, a "true" hepatic artery was not identified, but only a small arterial vessel measuring about 2 mm in diameter, just in front of the portal vein, apparently emerging from the parenchyma of the pancreatic head. To obtain complete mobilisation of the duodeno-pancreatic block from the portal vein, it was necessary to cut this small arterial vessel. In the postoperative period, the patient developed extensive liver ischaemia, which was gradually resolved, but resulted in multiple stenosis of the intra- and extra-hepatic biliary tree. At follow-up at three years, the patient was in fairly good condition, with a permanent percutaneous biliary drainage, but with no clinical or radiological signs of local or distant disease. Although interruption of hepatic arterial flow is usually well tolerated, this is not always the case. It is important to predict in what circumstances complications are likely to occur. The main determinants that should guide the surgeon faced with this problem are whether the portal circulation is normal, whether structures carrying collateral blood supply have been interrupted, and whether some form of biliary reconstruction is needed [483].

Extended lymphadenectomy

Several factors argue for extended lymphadenectomy in surgery for pancreatic adenocarcinoma: 1) lymph node extension is an adverse prognostic factor; 2) some tumor recurrences are only loco-regional suggesting that initial resection was insufficient; 3) some retrospective studies suggest that extension of lymphadenectomy improves post-resection survival. Extended lymphadenectomy, including circumferential dissection of both the celiac axis and the superior mesenteric artery and resection of para-aortic nodes, was evaluated by 4 randomized trials; globally there was no survival benefit. Extended lymphadenectomy increases, at least transiently, the risk of post-operative diarrhea. Its influence on the rate of loco-regional recurrences has not been evaluated. However, this technique should not be definitively and globally precluded since a more radical resection was associated with a trend toward better long-term survival in the trial with the largest number of patients [484].

Cryosurgery

To test the feasibility of cryosurgery for pancreatic carcinoma and to observe the consequence of cryosurgery by two different techniques. Twelve 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 ^{o}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. It was concluded that mild hypothermic cryosurgery with liquid nitrogen superficial refrigeration might lead to pancreatic injury and induce acute pancreatitis, yet deep hypothermic cryosurgery with adequate time showed a promising effect in destroying pancreatic tissue and preventing acute pancreatitis [485].

Postoperative complications

It was aimed to compare different techniques using the definitions of the International Study Group of Pancreatic Surgery for postoperative complications after pancreaticoduodenectomy. The perioperative data of 119 patients that underwent pancreaticoduodenectomy by a single surgeon were retrospectively analyzed. Pancreaticojejunal anastomosis was performed using the dunking method (n=39), the duct-to-mucosa anastomosis method (n=40), and the duct-to-mucosa adaptation (n=40). The most frequent complication was postoperative pancreatic fistula (POPF; grades A, 21 %; B, 8 %; and C, 3 %), postpancreatectomy hemorrhage (PPH; grades B, 7 % and C, 1 %), and delayed gastric emptying (DGE; grades A, 1 % and B, 6 %). No significant differences in POPF were found between patients who underwent different types of pancreatic anastomoses. Only pancreatic ductal adenocarcinoma and pancreatic texture were potentially related to POPF. Patients with or without POPF grade A had significantly shorter postoperative stays than patients with grade B or C POPF, and similar findings were obtained for DGE and PPH. It was concluded that the successful management of pancreatic anastomoses depends more on a meticulous surgical technique and appropriate experience rather than on the type of technique. Furthermore, the International Study Group of Pancreatic Surgery definitions of POPF, DGE, and PPH seem objective and universally acceptable [486].

Surgical results

Although a positive resection margin has been reported to be a strong prognostic factor after resection for pancreatic cancer, several studies indicated that resection status did not independently affect survival. The aim of one study was to examine the influence of resection margin status on survival after extended radical resection for pancreatic head cancer. One hundred thirty-eight cases of pancreatoduodenectomy and 38 cases of pylorus-preserving pancreatoduodenectomy for invasive ductal carcinoma of the pancreas were retrospectively analyzed. The resection margins were negative (R0) in 115 patients (65 %), microscopically positive (R1) in 38 patients (22 %), and grossly positive (R2) in 23 patients (13 %). Patients with R1 resection survived significantly shorter (median survival time, MST, 9 months) than R0 resection patients (MST, 15 months) but survived longer than R2 resection patients (MST, 6 months). By multivariate analysis, R2 resection, together with lymph node metastasis, portal venous system, and extrapancreatic nerve plexus invasions, independently affected the overall survival, but R1 resection was not significantly influential. It was concluded that R1 resection did not independently affect the survival [487].

The authors analysed the results of 363 patients, who underwent surgery for pancreatic or periampullary tumours. There were 175 operable and 188 inoperable cases. The preoperative data (age, gender, site of the tumour, characteristic clinical signs), as well as surgical methods are overviewed. A pancreatoduodenectomy was most frequently applied as

a curative surgery, while double-bypass was mainly performed for palliation. As far as postoperative complications, especially the rate of pancreatic fistula, which is influenced by the anastomotic method, were discussed. Reoperation and early postoperative mortality rate was 5.7 percent and 4.5 percent in the operable cases, respectively. These numbers were 1.6 percent and 6.9 percent among the inoperable cases [488].

Long-term survival

As surgeons, one may justifiably be proud of the significant role we have played in reducing both the morbidity and mortality of pancreatoduodenectomy within the past 20 years. But, as John Howard once stated, the surgeon's role in curing pancreatic ductal adenocarcinoma is limited to "a margin-negative resection, accomplished with minimal postoperative complications." It is apparent that other intrinsic factors determine the likelihood of actual cure. Rather than being disappointed at the low rate of eradication of disease, surgeons can take solace in being able to provide meaningful increases in the length of patient survival. To determine the actual eradication of disease rates for ductal adenocarcinoma of the pancreas treated by pancreatoduodenectomy, an extensive search of the literature was undertaken. Articles reporting actuarial survival rates were excluded, and only studies providing actual survival rates have been included in the analysis [489-498]. From the summarized data it can be reach several important conclusions. First, actual 5-year survival after "curative" pancreatoduodenectomy for ductal adenocarcinoma of the pancreas is not common, occurring in only 1 in 10 patients undergoing resection for "cure." Nevertheless, the 10 percent 5-year actual survival rate following pancreatoduodenectomy for ductal adenocarcinoma in this collected series is higher than many 5-year actual survival rates in previous reports. This may be due to the large percentage of R0 resections included in the the analysis. However, these results must also be tempered with the realization that 5-year survivors of ductal adenocarcinoma of the pancreas can occur without resection and have been well documented [499]. Furthermore, to place these collective survival results in an even broader perspective, the percentage of 5-year survivors would markedly diminish if the denominator were to be changed from R0 resections to R1 resections, or if the denominator included patients with adenocarcinoma of the body or tail of the gland. Another important conclusion from the data is that 5-year surgical survivors continue to expire from recurrent pancreatic adenocarcinoma as they are followed for longer periods. By 10 years after "curative" resection, the number of survivors from the original surgical population had decreased from 9.8 percent to 2.8 percent. Of course, not all of the deaths in the second 5-year observation period were due to recurrent pancreatic ductal adenocarcinoma, been expected to die after the 10-year mark, but deaths from recurrent adenocarcinoma of the pancreas have been known to occur more than 10 years after pancreatoduodenectomy [500, 501]. Using a life-table analysis of age-matched healthy controls, Riall et al [502] have estimated that, at some point in their course, 71 percent of 5-year surgical survivors will die of recurrent pancreatic ductal adenocarcinoma. Nevertheless, 20-year survivors after pancreatoduodenectomy for documented ductal adenocarcinoma of the pancreas have been reported. Almost certainly, some of these 10-year survivors either were living with recurrence or would develop recurrence in the future. It seems clear that the answer to the question of the likelihood of eventual surgical "cure" is "not very likely."

The aim of one study was to determine the survival of patients with advanced, unresectable pancreatic cancer in relation to whether they underwent nonsurgical biopsy of their primary tumor. A total of 1481 patients with distant stage pancreatic cancer diagnosed between 1992 and 2001 who underwent radiation treatment but not cancer-directed surgery were analyzed. The design is a retrospective cohort study from the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute. Of 1481 patients (median age, 66 years) included in our analysis, 1406 (95 %) underwent nonsurgical biopsy (95 %) and 75 (5 %) did not. There was no statistically significant difference in overall median survival

according to receipt of nonsurgical biopsy. A subgroup analysis of patients younger than 65 years who did not undergo biopsy revealed a hazard ratio of 1.76 (95 % confidence interval, 1.14 to 2.72); that is, there was a 76 percent higher hazard for death among younger patients who did not undergo biopsy compared with those who did. It was concluded that nonsurgical biopsy did not seem to negatively impact survival among patients with advanced pancreatic cancer [503].

Intrahepatic recurrent biliary tract stones
Intrahepatic biliary lithiasis is fairly rare in western countries. In a case described, liver stones had developed as a late consequence of biliary derivative surgery, which is well known to lead to this complication. However, this case is unusual because people who have undergone radical surgery for cancer of the head of the pancreas seldom survive long enough for liver stones to develop. Treatment for this 65-year-old woman, previously submitted to duodeno-cephalopancreatectomy, involved percutaneous balloon bilioplasty, with several passages in order to open the anastomosis. We then positioned two inner-outer biliary drains, through which repeated lavages were done. Finally, the patient underwent laser lithotripsy of the intrahepatic calculi and the fragments were cleared using a Dormia basket. Repeated cholangiographic monitoring showed progressively fewer stones, until the intrahepatic biliary tree was finally completely clear 120 days after the initial diagnosis. At the last follow-up, the patient was healthy, with normal blood values, considering her overall condition [504].

Body and tail tumors

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. It was concluded 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 [505].

Distal pancreatectomy

Pancreatic leak remains a major cause of postoperative morbidity in patients undergoing pancreatic resection. It was evaluated the incidence of and identify risk factors for the development of pancreatic leak in patients undergoing distal pancreatectomy (DP) at a single high-volume institution. All patients who underwent primary open distal pancreatectomy (excluding completion pancreatectomy and debridement) between 1984 and 2006 were identified, and their medical records were reviewed. In a cohort of 704 patients undergoing primary DP, the indications for distal pancreatectomy were benign pancreatic neoplasm (34 %), malignant pancreatic neoplasm (31 %), other neoplasm (15 %), chronic pancreatitis (14

%), pseudocyst (3 %), and trauma (3 %). The pancreatic remnant was sutured alone in 83 percent, stapled alone in 5 percent, and both stapled and sutured in 9 percent of cases. Ligation of the pancreatic duct was performed in 22 percent of cases. Perioperative mortality was <1 percent, but overall morbidity was 33 percent, most commonly pancreatic leak (12 % clinically significant, 21 % biochemical). Multivariable logistic regression analysis revealed that neither the method of closure of the pancreatic remnant nor ligation of the pancreatic duct affected the risk of clinically significant pancreatic leak. This largest reported series of distal pancreatectomy demonstrates that this procedure can be performed with low mortality but still carries a substantial risk of morbidity, particularly pancreatic leak. In contrast to some previous studies, this analysis found that surgical management of the pancreatic remnant has no effect on the incidence of clinically significant pancreatic leak [506].

The spleen may be preserved during distal pancreatectomy (DP) for benign disease. The aim of this study was to compare the perioperative and postoperative courses of patients with conventional DP and spleen-preserving distal pancreatectomy (SPDP) for benign lesions or tumors with low-grade malignant potential occurred at the body or tail of the pancreas. A retrospective analysis was performed for the hospital records of all the patients undergoing DP and SPDP between January 1995 and April 2006. One-hundred forty-three patients underwent DP and 37 patients underwent SPDP. There were no significant differences in age, sex, indications of operation, estimated blood loss, operative time, and postoperative hospital stay between the two groups. Pancreatic fistula occurred in 21 (13 %) patients following DP and in 3 (8 %) following SPDP without a significant difference. Portal vein thrombosis occurred in 4 patients after DP. Splenic infarction occurred in one patient after SPDP. Overwhelming postosplenectomy infection was observed in one patient after DP. SPDP can be achieved with no increase in complication rate, operative time, or length of postoperative hospitalization as compared to conventional DP. Additionally, it has the advantage of reducing the risk of overwhelming postsplenectomy infection and postoperative venous thrombosis [507].

Laparoscopic distal pancreatectomy

The last decade has seen an increase in the application of minimally invasive surgical procedures to the management of pancreatic disease. Laparoscopic pancreatic surgery is an advanced laparoscopic procedure with a significant learning curve. It should be considered only by surgeons with extensive experience in open pancreatic surgery who possess advanced laparoscopic skills. Early reports suggest that laparoscopic pancreatic surgery can be accomplished with acceptable morbidity and mortality for the resection of small benign and low-grade malignant lesions in the body and tail of the pancreas and for the internal drainage of pancreatic pseudocysts. Its role in the management of lesions in the head, neck, and uncinate process of the pancreas is yet to be determined [508].

Laparoscopic distal pancreatectomy (LP) is an emerging modality for managing benign and premalignant neoplasms of the pancreatic body and tail. The efficacy of LP has been examined in single and multi-institutional retrospective reviews but not compared prospectively to open distal pancreatectomy (ODP). Therefore, it was maintain a prospectively accruing database tracking peri-operative clinical parameters for all patients presenting to a tertiary care facility for treatment of pancreatic disease. It was queried this database for patients undergoing LP or ODP between 2003 and 2008. Preoperative, operative, and postoperative characteristics were compared using standard statistical methods. One-hundred twelve patients underwent distal pancreatectomy. Eighty-five underwent open distal pancreatectomy. Twenty-eight LPs were attempted and 27 completed laparoscopically. One LP was converted to an open procedure because of bleeding and was excluded from study. In comparison to ODP, patients undergoing LP had statistically similar

pre-operative demographics, disease comorbidities, tumor size, length of operation, rates of postoperative mortality, postoperative morbidity, and pancreatic fistula. Patients undergoing LP were less likely to have ductal adenocarcinoma and had fewer lymph nodes harvested in their resection but had a significantly shorter postoperative length of stay and significantly lower estimated blood loss than those undergoing ODP. It was concluded that laparoscopic distal pancreatectomy is a safe, effective modality for managing premalignant neoplasms of the pancreatic body and tail, providing a morbidity rate comparable to that for ODP and substantially shorter length of stay. Laparoscopic distal pancreatectomy fails to provide a lymphadenectomy comparable to open distal pancreatectomy. This may limit the applicability of laparoscopic distal pancreatectomy to the treatment of pancreatic adenocarcinoma [509].

Despite the relatively slow start of laparoscopic pancreatectomy relative to other laparoscopic resections, an increasing number of these procedures are being performed around the world. Operations that were once considered impossible to perform laparoscopically, such as pancreaticoduodenectomy and central pancreatectomy are gaining momentum. Technology continues to improve, as does surgical experience and prowess. There are both enough experience and data (though retrospective) to confirm that laparoscopic distal pancreatectomy with or without spleen preservation appears to be a safe treatment for benign or noninvasive lesions of the pancreas. Based on the fact that laparoscopic distal pancreatectomy can be performed with similar or shorter operative times, blood loss, complication rates, and length of hospital stay than open distal pancreatectomy, it can be recommended as the treatment of choice for benign and noninvasive lesions in experienced hands when clinically indicated. It is very difficult to make clear recommendations with regard to laparoscopic resection of malignant pancreatic tumors due to the lack of conclusive data. As long as margins are negative and lymph node clearance is within accepted standards, laparoscopic distal pancreatectomy appears to have no untoward oncologic effects on outcome. Certainly more data, preferably in the manner of a randomized clinical trial, are needed before additional recommendations can be made. Potential benefits of laparoscopic resection for cancer include the ability to inspect the abdomen and abort the procedure with minimal damage if occult metastases are identified. This does not delay the onset of palliative chemotherapy, which would be the primary treatment in that circumstance. In fact, there is evidence to suggest that there is a greater likelihood of receiving systemic therapy if a laparotomy is avoided in patients who have radiologically occult metastases. Patients may also undergo palliative laparoscopic gastric and biliary bypass if indicated. Faster wound healing may also translate into a shorter waiting time before initiating adjuvant chemotherapy and/or radiation therapy. If the patient develops a wound infection, the infection should be more readily manageable with smaller incisions. Although not proven clinically relevant in humans, the reduction in perioperative stress associated with laparoscopic resection may translate to a cancer benefit for some patients. One report compared markers of systemic inflammatory response in 15 subjects undergoing left pancreatectomy. Eight had hand-access laparoscopic procedures and the rest had standard open surgery. The subjects in the laparoscopic group had statistically lower C-reactive protein levels than the open group on postoperative days one (5.5 mg/dL versus 9.7 mg/dL) and three (8.5 mg/dL versus 17.7 mg/dL), suggesting that the laparoscopic approach to left pancreatectomy is associated with less inflammation. While this report is underpowered, it supports the notion that MIS cancer surgery may induce less of a systemic insult to the body than standard open cancer surgery. More work in this area is necessary before any firm conclusions can be drawn. An important issue to consider is that of training surgeons to perform these complex procedures laparoscopically. Not all pancreatectomies are amenable to the laparoscopic approach, even in the most skilled hands. As such, only a percentage of cases will be performed this way and expectations to educate surgeons adequately to perform advanced laparoscopic procedures can be unrealistic, resulting in more "on-the-job" training. Another aspect that draws some controversy is that of the totally laparoscopic procedure versus the hand-access approach. No laparoscopic instrument provides the tactile feedback possible to obtain with the hand. Finally, it is important to remember that if the

procedure is failing to progress laparoscopically, or if cancer surgery principles are likely to be violated, the surgeon (and the patient) must be willing to abort the laparoscopic approach and complete the operation using standard open technique. During the next few years we can expect to see more robust outcome data with laparoscopic pancreatectomy. The expectation is that more data will come to light demonstrating benefits of laparoscopic pancreatic resection as compared with open technique for selected patients. Several groups are considering randomized trials to look at these endpoints. Although more retrospective and prospectively maintained data will certainly be presented, it is less likely that randomized data specifically examining the question of laparoscopic versus open pancreatectomy for cancer will mature, due to some of the limitations discussed above. Additional areas of discovery are in staple line reinforcement for left pancreatectomy and suturing technology for pancreatico-intestinal anastomosis. Robotic surgery may have a role in pancreatic surgery. Improving optics and visualization with flexible endoscopes with provide novel surgical views potentially improving the safety of laparoscopy. Another area in laparoscopic surgery that is gaining momentum is that of Natural Orifice Transluminal Endoscopic Surgery (NOTES). NOTES represents the "holy grail" of incisionless surgery. Can we enucleate a small tumor off the pancreatic body by passing an endoscope through the gastric (or colonic) wall, and bring the specimen out via the mouth or anus? Can we use this approach for formal left pancreatectomies? Pioneers have already developed a porcine model of left pancreatectomy. This technology must clear several hurdles before it is cancer ready; however, technology is moving at a rapid pace [510].

Spleen-preserving laparoscopically

Laparoscopic resection for small lesions of the pancreas has recently gained popularity. It was reported the initial experience with a new approach to laparoscopic spleen-preserving distal pancreatectomy so that the maximum amount of normal pancreas can be preserved while ensuring adequate resection margins and preservation of the spleen and splenic vessels. Three patients underwent laparoscopic distal pancreatectomy with spleen and splenic vessel preservation over a 2-month period. Two patients underwent resection using the conventional medial-to-lateral dissection as the lesion was close to the body or proximal tail of the pancreas. The third patient had a lesion in the distal tail of the pancreas and surgery was carried out in a lateral-to-medial manner. This new approach minimized excessive sacrifice of normal pancreatic tissue for such distally located lesions. The splenic artery and vein were preserved in all cases and there was no significant difference in clinical outcome, operative time or intraoperative blood loss. It was concluded that although the conventional “medial-to-lateral” approach is recommended for more proximal tumours of the pancreas, distal lesions can be safely addressed using the “lateral-to-medial” approach [511].

NOTES

Natural orifice transluminal endoscopic surgery (NOTES) research has primarily involved case series reports of low-risk procedures. To compare endoscopic transgastric distal pancreatectomy (ETDP) and laparoscopic distal pancreatectomy a prospective trial in 41 swine, laparoscopic pancreatectomy was performed with 3 trocars and stapled transection of the pancreas. ETDP was performed via a gastrotomy, with 1 trocar for visualization, by using endoloop placement, snare transection, and purse-string gastrotomy closure. Swine were survived for 8 days. The procedure time for ETDP was significantly greater than for LDP. Pancreatic specimen weight was smilar. Postoperatively, 26 of 28 animals thrived. In the laparoscopic group, 1 death caused by pancreatic leak and renal failure occurred on day 1. In the ETDP group, 1 death caused by pneumothorax occurred intraoperatively. The necropsy, CT, and histologic examinations revealed focal resection-margin necrosis in 3 to 7 swine in the ETDP group with no proximal necrosis or pancreatitis. The groups were equivalent clinically, by survival, and by serum and peritoneal fluid analysis. The gastrotomy

closure was associated with small serosal adhesions, but no gross abscess or necrosis. Thus, there was no clinical or survival difference between NOTES and laparoscopic approaches [512].

Renal function at pancreatoduodenectomy

A retrospective study was conducted to compare measured creatinine clearance (Ccr) with estimated glomerular filtration rate (eGFR) as a preoperative renal function test in patients undergoing pancreatoduodenectomy. The records of 139 patients undergoing pancreatoduodenectomy were enrolled, and preoperative Ccr, 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 Ccr, eGFR3, and eGFR5. There were 30 patients with abnormal Ccr 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 Ccr abnormal level. The sensitivity and specificity of eGFR3 and eGFR5 for postoperative renal dysfunction were better than those of Ccr, and multivariate analysis showed that eGFR5 was the only independent predictive factor for postoperative renal dysfunction. Thus means that the eGFR5 and eGFR3, rather than the creatinine clearence, are recommended as preoperative renal function test in patients undergoing pancreatoduodenectomy [513].

Glucose monitoring

Peroperatively

To evaluate a closed-loop system providing continuous monitoring and strict control of perioperative blood glucose following pancreatic resection it was performed a prospective, randomized clinical trial in 30 patients who had pancreatic resection for pancreatic neoplasm. Perioperative blood glucose levels were continuously monitored using an artificial endocrine pancreas (STG-22). Glucose levels were controlled using either the sliding scale method (sliding scale group, n=13) or the artificial pancreas (artificial pancreas group, n=17). Incidence of severe hypoglycemia (<40 mg/dL) during the intensive care period following pancreatic resection in patients monitored with the artificial pancreas was recorded. The secondary outcome measure was the total amount of insulin required for glycemic control in the first 18 hours after pancreatic resection in each patient group.: In the sliding scale group, postoperative blood glucose levels rose initially before reaching a plateau of approximately 200 mg/dL between 4 and 6 hours after pancreatectomy. The levels remained high for 18 hours postoperatively. In the artificial pancreas group, blood glucose levels reduced steadily, reaching the target zone (80-110 mg/dL) by 6 hours after surgery. The total insulin dose administered per patient during the first postoperative 18 hours was significantly higher in the artificial pancreas group than the sliding scale group. Neither group showed hypoglycemia. It was concluded that perioperative use of an artificial endocrine pancreas to control pancreatogenic diabetes after pancreatic resection is an easy and effective way to maintain near-normal blood glucose levels. The artificial pancreas shows promise for use as insulin treatment for patients with pancreatogenic diabetes after pancreatic resection [514].

Glucos metabolism after pancreatectomy

The aim of this study was to investigate the mechanisms of the change in glucose metabolism after a pancreatoduodenectomy (PD). Oral glucose tolerance tests were performed in 17 patients before and 1 month after a PD. The changes in plasma glucose and insulin concentrations, homeostasis model of insulin resistance, and insulinogenic index (beta-cell function) were analyzed. Two additional factors, gastric emptying function and plasma glucagon-like peptide-1 (GLP-1) concentration that possibly affect perioperative glucose metabolism were also assessed. The plasma glucose and insulin concentrations were significantly lower after the operation, especially in preoperative diabetic patients. beta-Cell function did not change after the operation. On the other hand, insulin resistance became normal 1 month after the operation. The value of gastric emptying function after the operation was not statistically different in comparison with that before the operation. Postoperative plasma GLP-1 concentration was significantly higher than the preoperative value. It was concluded that beta-cell function is maintained after a pancreatoduodenectomy, whereas the improvement of insulin resistance may cause a short-term transient improvement of the glucose metabolism after the operation. The significance of increased postoperative GLP-1 concentration remains an unsolved issue [515].

Palliation

Inadequate nutrient intake is common in cancer patients and is associated with poor outcomes. Social factors may contribute to inadequate nutrient intake, although they have not been studied. The purpose of one study was to investigate social factors that may contribute to undereating in older adults with cancer. Participants included 30 patients, 17 women and 13 men, aged 70-99 years, who were diagnosed with pancreatic, colon, breast, lymphoma, skin, and head and neck cancers. Both participants and caregivers interpreted weight loss as a positive health outcome of cancer. Furthermore, some patients who had lost weight worked to keep the weight off by going on special diets. Patients and caregivers imbued certain foods with health-promoting qualities without corroborating scientific evidence. Cancer- and treatment-related alterations in self-identity due to changes in their bodies, in taste, and in the manner in which they must eat caused cancer patients to experience frustration and embarrassment, which led to reduced nutritional intake. Despite their compromised nutritional status, patients did not discuss food and eating habits with their physicians. Behaviors and attitudes of patients and caregivers may lead to negative changes in eating behaviors beyond the cancer itself or its treatment or sequelae. Many of these behaviors are potentially modifiable with appropriate education, communication, and intervention [516].

Palliative stenting

In the endoscopic management of unresectable malignant biliary obstructions by placement of a metallic stent, longer patency and a lower incidence of stent occlusion are desirable goals. With its mesh structure, the uncovered metallic stent is occluded mainly by tumor or tissue ingrowth, making it impossible to remove. The covered metallic stent was developed to overcome these disadvantages, and was shown to maintain patency longer than the uncovered in one randomized study. The most important characteristic of the covered stent is that it is removable, allowing it to be used in patients with resectable malignancies and benign strictures. In addition, the drug-eluting covered metallic stent provides an additional approach to the treatment of biliary malignancies. The covered stent may also change the treatment paradigm for biliary strictures and strictures due to chronic pancreatitis. The covered metallic stent is analogous to a large-bore, expandable plastic stent and is effective both as an endoprosthesis and a dilating or anti-cancer device. However, to better

understand the utility of these devices, one need to first consider mechanical properties such as radial force (expansion force) and axial force (straightening force) [517].

Endoscopic biliary drainage is widely accepted as palliative treatment in patients with pancreatic cancer. One study was designed to compare self-expanding metal stent and polyethylene stent in a homogeneous patient group with advanced pancreatic cancer. The study included 154 patients initially treated with a metal or plastic stent. Median survival time, stent patency, and stent-associated hospital admissions were evaluated. The median survival time in patients treated with metal and plastic stent was 6 and 4 months, respectively. Self-expanding metal stents have a significantly higher patency rate than polyethylene stents. Stent occlusion was observed in 21 (33 %) of 63 patients in the plastic stent group after a median period of 57 days and in 17 (19 %) of 91 patients in the metal stent group after a median period of 126 days. The total time of hospital stay after initial implantation of metal or plastic stent was 7 and 17 days, respectively. It was concluded that self-expanding metal stents have a longer patency than polyethylene stents. Additionally, the number of stent-associated hospital admissions and the total time of hospital stay were higher in the plastic stent group. The median survival time was not significantly different in both groups [518].

Prediction of survival

The pancreatic nomogram, originally developed in the Memorial Sloan-Kettering Cancer Center in the USA, combines clinicopathological and operative data to predict disease-specific survival at 1, 2 and 3 years from initial resection. An external patient cohort from a retrospective pancreatic adenocarcinoma database at the Academic Medical Centre in Amsterdam was used to test the validity of the pancreatic adenocarcinoma nomogram. The cohort included 263 consecutive patients who had surgery between 1985 and 2004. Data for all the necessary variables were available for 256 patients (97 %). At the last follow-up, 35 patients were alive, with a median follow-up of 27 (range 3-114) months. The 1-, 2- and 3-year disease-specific survival rates were 61, 30 and 16 percent respectively. The nomogram concordance index was 0.61. The calibration analysis of the model showed that the predicted survival did not significantly deviate from the actual survival. The Memorial Sloan-Kettering Cancer Center pancreatic cancer nomogram provided an accurate survival prediction. It may aid in counselling patients and in stratification of patients for clinical trials [519].

Identification of defined patient groups based on a prognostic index may improve the prediction of survival and selection of therapy for patients with pancreatic cancer. Many prognostic factors have been identified often based on retrospective, underpowered studies with unclear analyses. Data from 653 patients were analysed. Continuous variables are often simplified assuming a linear relationship with log hazard or introducing a step function (dichotomising). Misspecification may lead to inappropriate conclusions but has not been previously investigated in pancreatic cancer studies. Models based on standard assumptions were compared with a novel approach using nonlinear fractional polynomial transformations. The model based on fractional polynomial-transformed covariates was most appropriate and confirmed five previously reported prognostic factors: albumin, CA 19-9, alkaline phosphatase, LDH and metastases, and identified three additional factors not previously reported: WBC, AST and BUN. The effects of CA 19-9, alkaline phosphatase, AST and BUN may go unrecognised due to simplistic assumptions made in statistical modelling. We advocate a multivariable approach that uses information contained within continuous variables appropriately. The functional form of the relationship between continuous covariates and survival should always be assessed [520].

Quality of life

One study was designed to assess postoperative changes in the quality of life (QoL) of patients after surgical treatment for pancreatic cancer in a prospective single-centre study that included 54 patients with pancreatic cancer. Patients with potentially resectable tumours underwent pancreaticoduodenectomy (n=26), a double-bypass procedure (DBP) (n=17) or laparotomy (n=11). They were asked to complete a questionnaire before and at 1, 2, 3 and 6 months after surgery. QoL was assessed using the EORTC QLQ-C30 and EORTC QLQ-PAN26 questionnaires (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and PAN26). The patients did not demonstrate significant differences in the assessment of their global health status. Although, after resection, patients gave a positive assessment of most parameters in question, after DBP they reported some aggravation of most of the symptoms. The majority of patients did not have aggravated symptoms after laparotomy. It was concluded that the study had shown the value of conducting both curative and palliative resection for QoL. Bypass procedures should be performed in cases of non-resectable pancreatic cancer with accompanying jaundice and/or gastric outlet obstruction in patients with a life expectancy of at least 6 Montis [521].

Quality of care

Pancreatic cancer outcomes vary considerably among hospitals. Assessing pancreatic cancer care by using quality indicators could help reduce this variability. However, valid quality indicators are not currently available for pancreatic cancer management, and a composite assessment of the quality of pancreatic cancer care in the United States has not been done. Potential quality indicators were therefore identified from the literature, consensus guidelines, and interviews with experts. A panel of 20 pancreatic cancer experts ranked potential quality indicators for validity based on the RAND/UCLA Appropriateness Methodology. The rankings were rated as valid (high or moderate validity) or not valid. Adherence with valid indicators at both the patient and the hospital levels and a composite measure of adherence at the hospital level were assessed using data from the National Cancer Data Base (2004-2005) for 49 065 patients treated at 1134 hospitals. Summary statistics were calculated for each individual candidate quality indicator to assess the median ranking and distribution. Of the 50 potential quality indicators identified, 43 were rated as valid (29 as high and 14 as moderate validity). Of the 43 valid indicators, 11 (26 %) assessed structural factors, 19 (44 %) assessed clinical processes of care, four (9 %) assessed treatment appropriateness, four (9 %) assessed efficiency, and five (12 %) assessed outcomes. Patient-level adherence with individual indicators ranged from 50 percent to 97 percent, whereas hospital-level adherence with individual indicators ranged from 7 to 100 percent. Of the 10 component indicators (contributing 1 point each) that were used to develop the composite score, most hospitals were adherent with fewer than half of the indicators (median score = 4; interquartile range = 3-5). Based on the quality indicators developed in this study, there is considerable variability in the quality of pancreatic cancer care in the United States. Hospitals can use these indicators to evaluate the pancreatic cancer care they provide and to identify potential quality improvement opportunities [522].

Organization

The authors systematically reviewed the association between provider case volume and mortality in 101 publications involving greater than 1 million patients with esophageal, gastric, hepatic, pancreatic, colon, or rectal cancer, of whom more than 70,000 died. The majority of studies addressed the relation between hospital surgical case volume and short-term perioperative mortality. Few studies addressed surgeon case volume or evaluated long-term survival outcomes. Common methodologic limitations were failure to control for potential

confounders, post hoc categorization of provider volume, and unit of analysis errors. A significant volume effect was evident for the majority of gastrointestinal cancers; with each doubling of hospital case volume, the odds of perioperative death decreased by 0.1 to 0.23. The authors calculated that between 10 and 50 patients per year, depending on cancer type, needed to be moved from a "low-volume" hospital to a "high-volume" hospital to prevent 1 additional volume-associated perioperative death. Despite this, approximately one-third of all analyses did not find a significant volume effect on mortality. The heterogeneity of results from individual studies calls into question the validity of case volume as a proxy for care quality, and leads the authors to conclude that more direct quality measures and the validity of their use to inform policy should also be explored [523].

Chemotherapy

Gemcitabine has been standard therapy for advanced pancreatic cancer for well over a decade. The addition of capecitabine or erlotinib to gemcitabine has resulted in modestly improved, although still poor, overall survival. The majority of the recently completed randomized trials, however, have failed to demonstate an improvement of newer treatments over single-agent gemcitabine. Efforts currently underway center on new cytotoxic chemotherapy drugs, as well as novel targeted agents inhibiting various molecular pathways. Newly discovered proteins and cellular elements involved in tumor growth and invasion are potential therapeutic targets, and have become the focus of current trials, as well as future clinical trials. A better understanding of the biology of the disease at the basic science level, and epidemiology and risk factors from a public-health perspective, are needed. Continued research is clearly warranted with the goal of improving survival and optimizing treatment outcomes in locally advanced and metastatic pancreatic cancer [524].

Within a multi-centre, randomised phase II trial, 95 patients with locally advanced pancreatic cancer were assigned to three different chemoradiotherapy regimens: patients received conventionally fractionated radiotherapy of 50 Gy and were randomised to concurrent 5-fluorouracil (350 mg m^2 per day on each day of radiotherapy, RT-5-FU arm), concurrent gemcitabine (300 mg m^2), and cisplatin (30 mg m^2) on days 1, 8, 22, and 29 (RT-GC arm), or the same concurrent treatment followed by sequential full-dose gemcitabine (1000 mg m^2) and cisplatin (50 mg m^2) every 2 weeks (RT-GC+GC arm). Primary end point was the overall survival (OS) rate after 9 months. The 9-month OS rate was 58 percent in the RT-5-FU arm, 52 percent in the RT-GC arm, and 45 percent in the RT-GC+GC arm. Corresponding median survival times were 9.6, 9.3, and 7.3 months, respectively. The intent-to-treat response rate was 19, 22, and 13 percent, respectively. Median progression-free survival was estimated with 4.0, 5.6, and 6.0 months. Grade 3/4 haematological toxicities were more frequent in the two GC-containing arms, no grade 3/4 febrile neutropaenia was observed. This means that none of the three chemoradiotherapy regimens tested met the investigators' definition for efficacy; the median OS was similar to those previously reported with gemcitabine alone in locally advanced pancreatic cancer [525].

Adjuvants and neoadjuvants

Neoadjuvant radiochemotherapy

It was explored surgical results after neoadjuvant chemoradiation therapy (NACRT) for patients with pancreatic cancer that extended beyond the pancreas. Sixty-eight consecutive patients with pancreatic cancer who underwent pancreatic resection were included. Twenty-seven patients underwent surgical resection after NACRT (NACRT group). The other 41 patients were classified as surgery-alone group. Surgical results were compared in patients who underwent curative resection (R0/1) who were followed up for at least 25 months and underwent no adjuvant therapy. A significantly lower frequency of lymph node metastasis

was observed in the NACRT group. The frequency of residual tumor grading in the NACRT group was significantly different from that in surgery-alone (R0/1/2 %, 52/15/33 vs 22/51/27). In R0/1 cases, overall survival and disease-free survival rates in the NACRT group (n=18) were significantly longer than in surgery-alone (n=30). The rate of local recurrence in the NACRT group was significantly less than in surgery-alone (11 % vs 47 %). It was concluded that this single-institution experience indicates that neoadjuvant chemoradiation therapy is able to increase the resectability rate with clear margins and to decrease the rate of metastatic lymph nodes, resulting in improved prognosis of curative cases with pancreatic cancer that extended beyond the pancreas [526].

Adjuvant chemoradiation

The role of adjuvant chemoradiation therapy (CRT) in pancreatic cancer remains controversial. The primary aim of one study was therefore to determine if CRT improved survival in patients with resected pancreatic cancer in a large, multiinstitutional cohort of patients. Patients undergoing resection for pancreatic adenocarcinoma from seven academic medical institutions were included. Exclusion criteria included patients with T4 or M1 disease, R2 resection margin, preoperative therapy, chemotherapy alone, or if adjuvant therapy status was unknown. There were 747 patients included in the initial evaluation. Primary analysis was performed between patients that had surgery alone (n=374) and those receiving adjuvant CRT (n=299). Median follow-up time was 12 months and 15 months, respectively, for survivors. Median overall survival for patients receiving adjuvant CRT was significantly longer than for those undergoing operation alone (20 vs 15 months). On subset and multivariate analysis, adjuvant CRT demonstrated a significant survival advantage only among patients who had lymph node (LN)-positive disease (hazard ratio 0.48, 95 % CI 0.36 to 0.64) and not for LN-negative patients (hazard ratio 0.81, 95 % CI 0.56 to 1.18). Disease-free survival in patients with LN-negative disease who received adjuvant CRT was significantly worse than in patients who had surgery alone (15 months vs 19 months). Thus this large multiinstitutional study emphasizes the importance of analyzing subsets of patients with pancreas adenocarcinoma who have LN metastasis. Benefit of adjuvant CRT is seen only in patients with LN-positive disease, regardless of resection margin status. CRT in patients with LN-negative disease may contribute to reduced disease-free survival [527].

Pre- plus postoperative chemoradiation

To evaluate both the feasibility and efficacy of our combined therapy, which consisted of preoperative chemoradiation, surgery, and postoperative liver perfusion chemotherapy (LPC) for patients with T3 (extended beyond the pancreatic confines) cancer of the pankreas 38 patients with T3-pancreatic cancers consented to receive a combination of preoperative chemoradiation, surgery, and postoperative LPC 2002 to 2007. With the aid of 3D radiation planning, irradiation fields were constructed that included both the primary pancreatic tumor and retropancreatic tissues while taking care to exclude any section of the gastrointestinal tract. The total dose of radiation was 50 Gy (2 Gy x 25 fractions/5 weeks) and was administered in combination with gemcitabine treatments (1000 mg/m/week x 9/3 months). Preoperative restaging via computerized tomography and intraoperative inspection were used to determine if pancreatectomy was indicated. For resected cases, one catheter was placed into the gastroduodenal artery and another one into the superior mesenteric vein. Postoperatively, 5-FU (125 mg/day x 28 days) was infused via each of these 2 routes. Preoperative chemoradiation was completed for all 38 patients, including 3 patients who required gemcitabine-dose reduction. Seven patients (18 %) did not undergo surgical resection because either distant metastases or progressive local tumors had been detected after chemoradiation. The remaining 31 patients (82 %) underwent pancreatectomy plus postoperative perfusion chemotherapy, without postoperative or in-hospital mortality. The 5-year survival rate after pancreatectomy was 53 percent, with low incidences of both local recurrence (9 %) and liver metastasis (7 %). Postoperative histopathologic study revealed a marked degenerative change in cancer tissue, showing negative surgical margins (R0) for 30 patients (96 %) and negative nodal involvement for 28 patients (90 %) [528].

Adjuvant 5-FU

The ESPAC-1, ESPAC-1 plus, and early ESPAC-3(v1) results (458 randomized patients; 364 deaths) were used to estimate the effectiveness of adjuvant 5FU/FA vs resection alone for pancreatic cancer using meta-analysis. The pooled hazard ratio of 0.70 (95 % confidence interval 0.55 to 0.88), and the median survival of 23 (95 % confidence interval 20 to 27) months with 5FU/FA versus 17 (14 to 19) months with resection alone supports the use of adjuvant 5FU/FA in pancreatic cancer [529].

Liver perfusion chemotherapy (LPC) for pancreatic cancer has been rarely undertaken in a postoperative adjuvant setting. It was evaluated the feasibility and antitumor efficacy of LPC with 5-fluorouracil (5-FU) followed by gemcitabine treatment 27 consecutive patients who underwent pancreatic resection and subsequent LPC + gemcitabine treatment during a 3-year period. The liver was infused with 5-FU (125 mg/body per day per route) via both routes of hepatic artery and portal vein for more than 21 days. After that, gemcitabine (1000 mg/m^2) was administered biweekly. Portal vein thrombosis developed in 1 patient, but 89 percent of patients tolerated LPC for more than 21 days with no life-threatening complication. Systemic administration of gemcitabine was accomplished in 93 percent; however, 1 patient died of serious capillary leak syndrome. No grade 4 toxicity was recorded, except for that patient. Median survival time and disease-free survival were 28 and 25 months, respectively. Hepatic relapse was observed in 26 percent (n=7). Survival was in favor of paraaortic node-negative cases (n=20) with a 2-year survival of 69 percent. This adjuvant chemotherapy shows promising survival benefit and seems to be indicative to paraaortic node-negative tumors [530].

5-Fluorouracil-cisplatin chemoradiation

The aim of one study was to assess the outcome of patients who received neoadjuvant 5-fluorouracil-cisplatin chemoradiation (CRT) for stage I/III pancreatic adenocarcinoma. Eligible patients (n=101) received radiation therapy (45 Gy) associated with continuous infusion of 5-fluorouracil accompanied by a cisplatin bolus. Of the 102 patients enrolled in the study, 26 patients had progression of cancer during treatment and were deemed unresectable; 1 patient died during CRT of septic shock. Sixty-two of 75 remaining patients underwent pancreaticoduodenectomy. The overall median survival of all 102 patients in the study was 17 months, with a 5-year survival of 10 percent. For patients who underwent resection, the median survival was 23 months. Correspondingly, the median survival was 11 months for the 40 unresected patients. The 5-year survivals for resected and unresected patients were 18 and 0 percent, respectively. A complete pathological response to neoadjuvant CRT was noted for 8 patients (13 %). Margin and lymph node positivity was present in 5 (8 %) and 15 (24 %) patients, respectively. There was documented local recurrence in 8 (13 %) and distant recurrence in 36 (58 %) patients, with the liver being the most common site [531].

Adjuvant radiotherapy

The role of adjuvant radiotherapy (RT) for pancreatic cancer remains controversial despite the completion of three multi-institutional randomized trials. One study examined the survival impact of postoperative radiotherapy in a large population-based database. Patients with pancreatic cancer diagnosed from 1988 to 2003 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. The cohort was limited to patients who underwent resection of nonmetastatic disease to yield a population of 3252 patients. The primary end point was overall survival. Survival analyses were conducted using corrections for perioperative mortality as well as a propensity score analysis to account for baseline differences in patient characteristics. Multiple independent factors were significantly associated with RT use, including patient age and disease stage. In general, younger patients and those with more advanced disease were more likely to receive radiotherapy. Disease stage significantly affected survival. For patients who survived at least 6 months, adjuvant RT was associated with increased survival (hazard ratio, 0.87; 95 % confidence

interval 0.80 to 0.96]. On subgroup analysis, only stage IIB (T1-3N1) patients enjoyed a statistically significant benefit associated with radiotherapy (hazaed ratio, 0.70; 95 % confidence interval 0.62 to 0.79). Although radiotherapy is associated with a survival benefit for nonmetastatic patients as a whole, this trend appears to predominantly derive from a survival benefit in patients with stage IIB disease [532].

Adjuvants among elderly

It was conducted a population-based study to describe the utilization, determinants, and survival effects of adjuvant therapies after surgery among older patients with pancreatic cancer. Using Surveillance, Epidemiology, and End Results-Medicare data, it was identified patients older than 65 years who received surgical resection for pancreatic cancer during 1992-2002. Approximately 49 percent of patients received adjuvant therapy after surgery. Patient factors associated with increased receipt of adjuvant therapy included more recent diagnosis, younger age, stage II disease, higher income, and geographic location. Hospital factors associated with increased receipt of adjuvant therapy included cooperative group membership and larger size. Adjuvant treatments associated with a significant reduction in 2-year mortality (relative to surgery alone) were chemoradiation or radiation alone but not chemotherapy alone. The findings suggest that adjuvant chemoradiation and, to a lesser degree, radiation only are associated with a reduction in the risk of mortality among older patients who undergo surgery for pancreatic cancer. However, receipt of adjuvant therapy varied by period and geography as well as by certain patient and hospital factors [533].

Palliative cytotoxic treatment

Evaluation of effects

A study was conducted to assess changes in tumor vascularity using contrast-enhanced ultrasonography in patients with pancreatic carcinoma under systemic chemotherapy and to examine the correlation among vascular change, clinicopathologic factors, and outcome. Forty-one consecutive patients with histopathologically confirmed pancreatic carcinoma who had distant metastases and were under systemic chemotherapy were recruited. Contrast-enhanced ultrasonography was performed before and after 1 and 2 cycles of treatment.The vascular signals from the tumor were continuously recorded,and the highest signal intensity was selected and classified into 5 categories by their intensity. As for the tumor response determined by dynamic computed tomography after 2 cycles, 6 patients showed a partial response, 25 remained stable, and in 10 patients, the disease progressed. A significant relationship was observed between vascular change after 1 cycle and tumor response. Progression-free survival and overall survival were significantly short in the case of patients showing increased vascularity after 1 and 2 cycles of chemotherapy, compared with those who did not. It was concluded that contrast-enhanced ultrasonography was useful to evaluate tumor vascular changes and thereby the effect of systemic chemotherapy, as well as the prognosis of patients with advanced pancreatic carcinoma [534].

Gemcitabine

Gemcitabine is an anti-cancer drug known to be safe and effective for pancreatic or biliary tract cancers, but lung injury is also known to be a rare side effect that sometimes becomes severe. It was report seven cases of lung injury during gemcitabine treatment. Drug-induced lung injury was suspected in all cases. The male : female ratio was 5:2, and the average patient age was 71. Four had pancreatic cancers and three had biliary tract cancers. Gemcitabine had been administered an average 5.9 times at a dose of 1141 mg. Patients showed a diffuse or patchy shadow mainly in the lower lung on computed tomography examination. Grades of adverse events were greater than 3 in all cases. Three patients died of the lung injury. Five cases had pulmonary emphysema, 2 had metastatic lung tumor as underlying pulmonary lesions, and these were assumed to have been important risk factors for drug-induced interstitial lung injury during gemcitabine treatment [535].

A 67-year-old male with pancreatic cancer (cStage IVb) was given gemcitabine on days 1, 8 and 15, and this was repeated on 29 days at dose of 800 mg/m(2) in outpatient clinic. After 2 courses, he suffered from dyspnea and fever. Laboratory examination showed that the serum levels of white cell count, C-reactive protein, lactate dehydrogenase and KL-6 were elevated. Chest X-ray and CT revealed diffuse bilateral interstitial infiltrates. He was diagnosed with drug induced interstitial pneumonia due to gemcitabine. Corticosteroid therapy consisting of methylprednisolone (1,000 mg/day) for three days followed by prednisolone was effective and he was discharged on the 29th day after admission. Acute pulmonary toxicity induced by gemcitabine could lead to severe complication [536].

Gemcitabine plus cisplatin

The antitumor activity and toxicity of a multi-step treatment were evaluated in patients with locally advanced, inoperable, or incompletely resected adenocarcinomas in 54 patients, 63 percent with pancreatic cancer and 37 percent with biliary tract tumors. The patients received 3 courses of cisplatin-gemcitabine induction chemotherapy. Progression-free (PF) patients were given consolidation radiotherapy with concurrent capecitabine. PF patients had, as maintenance immunotherapy interleukin 2 (1.8 x 106 IU) and 13-cis-retinoic acid (5 mg/kg). Thirty-eight patients, 27 with pancreatic and 11 with biliary tract adenocarcinomas, PF after cisplatin/gemcitabine, were treated with consolidation radiotherapy with concurrent capecitabine. Fourteen progressive free patients, 7 with pancreatic and 7 with biliary tract cancers, received maintenance immunotherapy. Median PF and overall survivals (OS) for all 54 patients were 7 and 12 months, respectively. Patients treated with maintenance immunotherapy had a median PF survival of 16 months, whereas median OS had not been reached yet, after a median follow-up of 28 months. Toxicity grades 3 and 4 for hematological and gastrointestinal was seen in 30 and 37 percent of patients, respectively; grades 1 and 2 autoimmune reactions were seen in 28 percent of patients. It was concluded that these results support the efficacy and safety of a multi-step sequential treatment in patients with locally advanced, inoperable or incompletely resected pancreatic and biliary tract adenocarcinomas [537].

Gemcitabine plus S-1

The patient was a 54-year-old male. He underwent resection of the pancreatic body tail region to treat pancreatic body tail cancer. On histopathological examination, the stump of the extirpated specimen was positive for tumor cells. After surgery, 10 courses of therapy with gemcitabine hydrochloride (GEM, 1, 000 mg/m^2, 3-week administration followed by 1-week discontinuation) were performed, and follow-up was continued. When a local relapse was detected chemotherapy with GEM was administered for 1 year and 9 months. However, when an increase in the recurrent lesion size and right lung metastasis were noted the regimen was switched to combination therapy with S-1 and GEM (S-1 60 mg/m^2 day, continuous administration on days 1 to 14 and 2-week discontinuation; and GEM 1, 000 mg/m^2, administered on days 8 and 15). After the end of the 11th course, PET-CT revealed the disappearance of FDG accumulation in the recurrent and metastatic lesion sites. During the treatment period, there were no grade 3 or higher adverse reactions [538].

A retrospective study aimed to evaluate the anti-tumor activity and toxicity of combination chemotherapy with gemcitabine (GEM) and oral S-1 or UFT in patients with advanced or metastatic pancreatic cancer. Ninety-four patients received chemotherapy. Among them, sixty-three were treated with GEM alone, twenty-two with UFT and GEM (UFT/GEM), and nine with S-1 and GEM (S-1/GEM). The median survival time was 9 months with GEM, 7 months with UFT/GEM, and 23 months with S-1/GEM. The overall response rate was 11 percent, 10 percent, and 22 percent, respectively. The 1-year survival rate was 30 percent, 36 percent, and 86 percent, respectively. Although the treatment-related adverse effects were not infrequent in patients treated with S-1/GEM, they were moderate in intensity. The combination chemotherapy with S-1/GEM was well tolerated and yielded a high response

rate in patients with pancreatic cancer [539].

Gemcitabine and iridotecan
Single-agent gemcitabine has been established as standard treatment for advanced pancreatic cancer since clinical studies have shown an improvement in overall survival and significant clinical benefit when compared to the best supportive care despite low overall objective response. Several phase II studies have tested other single agents and different gemcitabine-based regimens in pancreatic cancer, but both response and survival rates have remained low. Irinotecan, a topoisomerase I inhibitor currently approved for the treatment of metastatic colon cancer, has also demonstrated improved response rate in patients with pancreatic cancer. Our purpose was to determine the activity and toxicity of this regimen in patients with The or metastatic pancreatic cancer. Patients with histologically confirmed pancreatic adenocarcinoma received gemcitabine 1000 mg/m^2 plus irinotecan 100 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle for 6-8 months. From 2004 to 2006, 33 patients were entered into this study, 32 of whom were evaluable for treatment response, toxicity, median time to progression, and median survival. Characteristics included a median age of 63 years (range 41-79). One patient discontinued treatment due to adverse effects. The total number of cycles administered was 188 and the median number of cycles for patients was 6 (range 2-7). Thirty-two patients were assessable for toxicity and response. Grade 3 hematological toxicity occurred in 9 percent of patients and was primarily neutropenia. No grade >2 gastrointestinal toxicities or death due to treatment were observed. The most frequent nonhematological adverse event was fatigue. Ten patients responded to treatment with two complete responses (6 %) and eight partial responses (25 %), for an overall response rate of 31 percent; 11 patients achieved stable disease (34 %). The median time to tumor progression and the median survival were 9 (95 % confidence interval 6.0 to 12.4) and 12 (95 % confidence interval 7.7 to 15.9) months, respectively, with a 2-year survival of 22 percent. On the basis of this trial, the combination of gemcitabine plus irinotecan, administered in a weekly schedule and at this dose, is well tolerated and offers encouraging activity in the treatment of advanced and/or metastatic pancreatic cancer [540].

Gemcitabine and proton irradiation
One study evaluated the efficacy of combining proton irradiation with gemcitabine, and the role the inhibitor of apoptosis proteins survivin and X-linked inhibitor of apoptosis protein (XIAP) play in the radiosensitive versus radioresistant status of pancreatic cancer. The radioresistant (PANC-1) and radiosensitive (MIA PaCa-2) pancreatic carcinoma cells' response to combined gemcitabine and proton irradiation was compared. Gemcitabine and proton irradiation resulted in increased survivin levels with little apoptosis. However, combination therapy resulted in robust apoptotic induction with a concomitant survivin and XIAP reduction in the MIA PaCa-2 cells with little effect in the PANC-1 cells. Small interfering RNA studies confirmed a role for XIAP in the radioresistance of PANC-1 cells. The data demonstrate that combining gemcitabine and proton irradiation enhances apoptosis in human pancreatic cancer cells when XIAP levels decrease. Therefore, XIAP may play an important role in human pancreatic cancer proton radioresistance [541].

Gemcitabine experimentally
A test the efficacy of liposomal gemcitabine (GemLip) on primary tumor and metastases using the pancreatic tumor cell line AsPC1 implanted orthotopically into nude mice was made. In vitro, the IC_{50}s for GemLip and gemcitabine were 20 nM and 140 nM, respectively. However, when applied against established tumors, GemLip (8 mg/kg) blocked tumor growth for 5 consecutive weeks according to bioluminescence measurements in vivo. Gemcitabine (240 mg/kg) had no effect on luciferase-monitored tumor growth. When analyzed at the time of necropsy, GemLip strongly reduced tumor size, whereas gemcitabine only weakly affected tumor size. Empty liposomes had no effect on the tumor size. GemLip and empty liposomes both significantly interfered with the metastatic spread to the liver, as measured using luciferase assays. In addition, they showed effects against spleen, as well as peritoneal

metastases [542].

5-Fluorouracil
Twenty-one patients with unresectable locally advanced pancreatic cancer were evaluated in this retrospective analysis. They received extra-beam radiotherapy (50.4-54 Gy/28-30 fractions) with concurrent continuous infusion of 5-FU(250 mg/m^2 day) between 1999 and 2007. The radiation field included primary tumor and adjacent lymph nodes. Twenty patients (95 %) completed chemoradiotherapy, whereas one patient quit radiotherapy due to vomiting. No lethal side effects were observed. The response rate was 10 percent. One of the patients judged to have stable disease underwent resection after maintenance chemotherapy. The median progression free survival and the median overall survival were 6 and 12 months, respectively. In eleven patients (52 %), the initial sites of disease progression were local or peritoneum without liver metastases, suggesting systemic effects of this treatment. In conclusion, the authors said that 5-FU based chemoradiotherapyis well tolerated and provides definite benefits against unresectable locally advanced pancreatic cancer [543].

Oxaliplatin plus 5-fluorouracil
A phase II study was performed to assess the activity of oxaliplatin plus 5-fluorouracil (5-FU) modulated by leucovorin, as second-line treatment in locally advanced or metastatic pancreas adenocarcinoma pretreated with gemcitabine-containing schedule. Patients received weekly intravenous infusions of oxaliplatin 40 mg/m^2, 5-FU 500 mg/m^2, and leucovorin 250 mg/m^2 (3 weeks on, 1 week off). Twenty-three patients affected with metastatic (16) or locally advanced (7) pancreas adenocarcinoma were involved in this study. A total of 148 weeks of chemotherapy was delivered (median 2 courses each patient). Among 17 assessable patients, no objective response was registered and 4 patients had stable disease, whereas 13 had tumor progression. Median duration of stable disease was 14 weeks. Median time to progression of disease (TTP) was 12 weeks [95 % confidence interval 8 to 16]. Kaplan-Meier estimated median overall survival (OS) was 17 week (95 % confidence interval 4 to 30) and 3 months survival rate was 70 percent. Seven patients experienced grade 3 to 4 toxicity. The regimen was associated with 36 percent clinical benefit [544].

Capcitabine and celeoxib
It was evaluated a fully oral regimen of capecitabine and celecoxib (CapCel) as second-line treatment in 35 patients with documented progressive pancreatic cancer after first-line treatment were enrolled. Capecitabine was administered at a dose of 1,000 mg/m^2 b.i.d. for 2 consecutive weeks followed by 1 week of rest; celecoxib was given continuously at 200 mg b.i.d. Progression-free survival at 3 months was the primary study endpoint. The CapCel combination was associated with an overall response rate of 9 percent and median survival duration of 19 weeks. Sixty percent of patients were free from progression 3 months after the start of treatment. Multivariate analysis identified a positive clinical benefit response and a decline in CA 19.9 serum levels >25 percent compared with baseline levels as independent predictors of prolonged survival. The treatment protocol was well tolerated with negligible hematological toxicity. The most common grade 3 non-hematological toxicities were hypertransaminasemia, diarrhea and asthenia. It was concluded that CapCel combination is a safe treatment option with moderate activity in patients with pancreatic/biliary tract cancer after failure of a previous gemcitabine-containing regimen [545].

Gemcitabine plus uracil-tegafur and cyclophosphamide
In a retrospective analysis, it was compared the effectiveness and tolerability of gemcitabine (GEM) plus uracil/tegafur and cyclophosphamide with single-agent GEM as 1st-line chemotherapy for unresectable or recurrent pancreatic cancer. Thirty-three patients received combination therapy and 25 patients were treated with GEM alone. Tumor response rate was 14 percent versus 9 percent, median progression-free survival was 3 versus 4 months, and

median survival time was 7 versus 7 months in the combination and GEM groups, respectively. Complete response was observed just in 2 cases of the combination group, and 1 of them has been relapse-free for 3 years. In a subgroup of patients with good performance status, combination therapy prolonged median survival time significantly (9 vs 6 months). This combination therapy is well tolerated and may provide superior benefits to GEM monotherapy [546].

Uracil-tegafur

It was reported a case of pancreas head cancer with liver metastasis treated with uracil-tegafur (UFT) and gemcitabine combined chemotherapy. The histopathological diagnosis was adenocarcinoma, so it was inserted a self-expandable metallic stent (EMS) in this inoperable pancreas head cancer. It was performed nine courses of UFT and gemcitabine (GEM) combination chemotherapy. Renewed liver metastases did not appear, and the pancreas head tumor partially responded. Pancreatoduodenectomy was performed. After treatment with an additional 11 courses of chemotherapy, it was given S-1 orally because of a tumor recurrence. The patient survived for 24 months from the first laparotomy [547].

FOLFOX

Only a few clinical trials have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine-based chemotherapy. Therefore, there is no current consensus on the treatment of these patients. It was conducted a randomised phase II study of the modified FOLFIRI.3 (mFOLFIRI.3; a regimen combining 5-fluorouracil (5-FU), folinic acid, and irinotecan) and modified FOLFOX (mFOLFOX; a regimen combining folinic acid, 5-FU, and oxaliplatin) regimens as second-line treatments in patients with gemcitabine-refractory pancreatic cancer. The primary end point was the 6-month overall survival rate. The mFOlFIRI.3 regimen consisted of irinotecan (70 mg m^2; days 1 and 3), leucovorin (400 mg m^2; day 1), and 5-FU (2000 mg m^2; days 1 and 2) every 2 weeks. The mFOLFOX regimen was composed of oxaliplatin (85 mg m^2; day 1), leucovorin (400 mg m^2; day 1), and 5-FU (2000 mg m^2; days 1 and 2) every 2 weeks. Sixty-one patients were randomised to mFOLFIRI.3 (n=31) or mFOLFOX (n=30) regimen. The six-month survival rates were 27 percent (95 % confidence interval 13 to 46 %) and 30 percent (95 % confidence interval 15 to 49 %), respectively. The median overall survival periods were 17 and 15 weeks, respectively. Disease control was achieved in 23 percent (95 % confidence interval 10 to 42 %) and 17 percent of the patients (95 % confidence interval 6 to 35 %), respectively. The number of patients with at least one grade 3/4 toxicity was identical (11 patients, 38 %) in both groups: neutropenia (7 patients under mFOLFIRI.3 regimen vs 6 patients under mFOLFOX regimen), asthaenia (1 vs 4), vomiting (3 in both), diarrhoea (2 vs 0), and mucositis (1 vs 2). It was concluded that both mFOLFIRI.3 and mFOLFOX regimens were tolerated with manageable toxicity, offering modest activities as second-line treatments for patients with advanced pancreatic cancer, previously treated with gemcitabine [548].

Flavopiridol

Pancreatic adenocarcinoma harbors frequent alterations in p16, resulting in cell cycle dysregulation. A phase I study of docetaxel and flavopiridol, a pan-cyclin-dependent kinase inhibitor, demonstrated encouraging clinical activity in pancreatic cancer. This phase II study was designed to further define the efficacy and toxicity of this regimen in patients with previously treated pancreatic cancer. Patients with gemcitabine-refractory, metastatic pancreatic cancer were treated with docetaxel 35 mg/m^2 followed by flavopiridol 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Tumor measurements were performed every two cycles. Ten patients were enrolled, and 9 were evaluable for response. No objective responses were observed; however, 3 patients (33 %) achieved transient stable disease, with one of these patients achieving a 20 percent reduction in tumor size. Median survival was 4 months, with no patients alive at the time of analysis. Adverse events were significant, with 7 patients (78 %) requiring >1 dose reduction for transaminitis (11 %), grade 4 neutropenia (33 %), grade 3 fatigue (44 %), and grade 3 diarrhea (22 %). It was concluded that the combination of

flavopiridol and docetaxel has minimal activity and significant toxicity in this patient population. These results reflect the challenges of treating patients with pancreatic cancer in a second-line setting where the risk/benefit equation is tightly balanced [549].

S-1

The prognosis for advanced pancreatic cancer with peritoneal dissemination is extremely poor, and no effective standard therapy has been established. It was presented a case of a very old patient whose quality of life improved shortly after administration of only S-1 to treat advanced pancreatic cancer with peritoneal dissemination. Considering his general condition due to old age, the regimen for oral S-1 (80 mg/body/day) was set at 4 consecutive weeks of administration followed by a 2-week rest period. His abdominal circumference decreased and his appetite improved by 14 days following commencement of the therapy. The blood examination one month following commencement showed a significant decrease in the tumor marker. There was no adverse drug reaction. Six months later CT scanning showed that the ascites had disappeared and that the low-density area at the tail of the pancreas had become less obvious. The tumor marker and biochemical parameters were within standard ranges. Twelve months since the therapy began: there still has been no adverse drug reaction and his quality of life has been good [550].

EGFR-inhibitor

It was evaluated the epidermal growth factor receptor (EGFR) inhibitor gefitinib and docetaxel in a phase II study following gemcitabine failure. EGFR overexpression was not required. The initial docetaxel dose was 75 mg/m^2 on day 1 every 21 days. Due to febrile neutropenia in 8 of the first 18 patients, the dose was reduced to 60 mg/m^2. Gefitinib, 250 mg/day orally, was given continuously. Forty-one patients received treatment and were evaluable. Febrile neutropenia was seen in 11 patients (27 %), with most events occurring at the docetaxel dose of 75 mg/m^2 (8 of 18 patients). Common treatment-related grade 3/4 toxicities were: fatigue (7 %), nausea (7 %), diarrhea (5 %) and vomiting (2 %). There was 1 partial response and stable disease in 19 patients. Time to progression was 2 months and median survival was 5 months (95 % confidence interval 2.9-5.7). This means that the combination of gefitinib and docetaxel showed evidence of limited efficacy [551].

Radiotherapy with 5-FU, Gemcitabine or S-1

In one study, it was examined the safety and efficacy of chemoradiation in cases with local recurrence of pancreatic or biliary cancer after primary resection. Seven consecutive patients with recurrence of carcinoma of pancreas (n=3) and biliary system (n =4) were treated chemoradiotherapy. Local recurrence occurred around the portal vein in 6 patients and remnant pancreas in one patient respectively. Disease free survival after primary surgery was 22 months (range: 5-84). All patients received 50 Gy of conformal three-dimensional radiotherapy with concurrent 5-FU, Gemcitabine or S-1. Grade 3 of anorexia and elevation of transaminase level occurred in one patient respectively. Local tumor response was observed in two patients of pancreatic and biliary cancer respectively. Median survival calculated from the start of the chemoradiotherapy was 15 months (range: 6-24) in pancreatic cancer and 14 months (range: 11-20)in biliary cancer. The data suggest that chemoradiotherapy is feasible and effective treatment option in patients who present local recurrence after primary surgery in pancreatic or biliary cancer [552].

Immunotherapy

Dendritic cell (DC) therapy frequently induces a measurable immune response. However clinical responses are seen in a minority of patients, presumably due to insufficient expansion of antigen-specific cytotoxic T lymphocytes (CTLs) capable of eradicating tumor cells. To increase therapeutic efficacy of DC-based vaccination, we have undertaken the first clinical trial involving a combination therapy of gemcitabine (GEM) with immunotherapy for patients with inoperable locally advanced pancreatic cancer. Five patients received the treatment course, which consisted of intravenous GEM administration at 1000 mg/m^2 (day 1)

and the endoscopic ultrasound-guided fine-needle injection of OK432-pulsed DCs into a tumor, followed by intravenous infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody (CD3-LAKs) (day 4), at 2-week intervals. No serious treatment-related adverse events were observed during the study period. Three of the 5 patients demonstrated effective responses to this clinical trial; 1 had partial remission and 2 had long stable disease more than 6 months. In the patient with partial remission, it has been shown that DC-based vaccination combined with GEM administration induces tumor antigen-specific CTLs. It was concluded that combined therapy was considered to be synergistically effective and may have a role in the therapy of pancreatic cancer for inducing tumor antigen-specific CTLs [553].

Anti-gastrins

The experience of synthesising a novel gastrin receptor antagonist gastrazole and taking it into 3 small clinical studies in pancreatic cancer in man is described. The need for such a compound is illustrated by the observation that inhibition of gastric acid secretion by H2 receptor antagonists results in hypergastrinaemia. A large number of cell types have gastrin receptors including pancreatic cancer cells which have been shown to be stimulated by gastrin. Small numbers of pancreatic cancer patients given gastrazole by continuous intravenous infusion showed prolonged survival compared with best supportive care or placebo, and equivalent survival to those given 5 fluouracil. The results suggest a greater benefit for patients with early stage disease. An alternative gastrin receptor antagonist YF 476 is also described which has the advantage of efficacy given by the oral route. This new compound requires to be studied in pancreatic cancer and other diseases associated with hypergastrinaemia [554].

Monoclonal antibodies

Radiolabeled PAM4 IgG, a monoclonal antibody that recognizes a unique epitope associated with a mucin found almost exclusively in pancreatic cancer, has shown encouraging therapeutic effects in animal models and in early clinical testing (^{90}Y-humanized PAM4 IgG, ^{90}Y-clivatuzumab tetraxetan). The studies reported herein examine a new pretargeting procedure for delivering therapeutic radionuclides. It was shown that PAM4-based PT-RAIT with ^{90}Y hapten peptide is an effective treatment for pancreatic cancer, with less toxicity than ^{90}Y-PAM4 IgG, in this model. Combinations with gemcitabine and dose fractionation of the PT-RAIT enhanced therapeutic responses [555].

REG4 as predictive agent

Preoperative chemoradiotherapy is one of the key strategies for the improvement of survival in pancreatic cancer; however, no method to predict the response has yet been established. The aim of one study was to prospectively evaluate the predictive value of REG4, a new member of the regenerating (REG) islet-derived family of proteins. Stably REG4-expressing cells were established from a pancreatic cancer cell line and exposed in vitro to gamma-ray or gemcitabine to investigate the relevance of REG4 to the resistance to chemotherapy or radiotherapy. In 23 patients with resectable pancreatic cancer, the serum concentration of REG4 was measured before preoperative chemoradiotherapy, and the histologic response was evaluated after the surgery. A 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay and fluorescence activated cell scanning (FACS) revealed that REG4-overexpressing cells were resistant to gamma-radiation but showed a modest resistance to gemcitabine. The patients with a higher REG4 level, but not carcinoembryonic antigen or CA-19-9, showed an unfavorable histologic response to chemoradiotherapy. The patients showing a higher REG4 level experienced local recurrence postoperatively. These data demonstrated in vitro and in vivo that REG4 protein overexpression was associated with an unfavorable response to preoperative chemoradiotherapy. REG4 can clinically be used as a predictive biomarker [556].

Inhibition by propranolol

Propranolol inhibited pancreatic cancer cell proliferation by blocking signaling through the beta-adrenoceptor. It was hypothesized that propranolol may suppress pancreatic cancer cell growth through induction of apoptosis. The beta-adrenoceptor antagonist propranolol, beta1-adrenoceptor antagonist metoprolol, and beta2-adrenoceptor antagonist butoxamine were used to induce apoptosis in pancreatic cancer cells. The mRNA and protein expression of beta1- and beta2-adrenoceptors was analyzed using reverse transcriptase-polymerase chain reaction and Western blot. The pancreatic cancer cell line expressed mRNA and protein for both of beta1- and beta2-adrenoceptors. The Hoechst staining, TUNEL, and flow cytometry assay documented that the 3 drugs increased the number of apoptotic cells; the rate of apoptosis was the highest using butoxamine followed by propranolol, whereas the least was using metoprolol. beta-Adrenoceptor antagonists therapy affected caspase 3 and caspase 9 expression. It was concluded that the rate of apoptosis in pancreatic cancer cells was higher after treatment with butoxamine than propranolol, suggesting that propranolol induces apoptosis in pancreatic cancer cells via the beta2-adrenoceptors principally [557].

Hyperthermia

The aim of one study was to evaluate the efficacy and toxicity of concurrent chemoradiotherapy (CRT) with gemcitabine plus regional hyperthermia (HT) for locally advanced pancreatic carcinoma. A total of 29 patients with locally advanced pancreatic cancer treated with concurrent CRT using gemcitabine were retrospectively analyzed. Radiotherapy was administered with a median total dose of 61 Gy. Of the 29 patients, 20 (69 %) also underwent regional HT during CRT (CRHT group). The remaining 9 patients did not receive regional HT (CRT group) because of a common bile duct stent placement, patient refusal, older age, or obesity. The efficacy and toxicity of the treatments and the predictors of good outcome were evaluated. The median disease progression-free and overall survival times were significantly better for the CRHT group than for the CRT group (9 vs 5months, and 19 vs 10 months), respectively. Grade 3-4 hematological toxicities for the CRHT group were detected in eight patients (40 %) and grade 3 nonhematologic toxicity in one (diarrhea) [558].

Radiochemoradiation

It was presented an overview of phase III trials in adjuvant therapy for pancreatic cancer and reviewed outcomes at the Mayo Clinic after adjuvant radiochemotherapy (RT/CT) for resected pancreatic cancer. A literature review and a retrospective review of 472 patients who underwent an R0 resection for T1-3N0-1M0 invasive carcinoma of the pancreas from 1975 to 2005 at the Mayo Clinic, Rochester, MN, was performed. Patients with metastatic or unresectable disease at the time of surgery, positive surgical margins, or indolent tumors and those treated with intraoperative radiotherapy were excluded from the analysis. Median radiotherapy dose was 50.4 Gy in 28 fractions, with 98 percent of patients receiving concurrent 5-fluorouracil-based chemotherapy. Median follow-up was 2.7 years. Median overall survival (OS) was 1.8 years. Median OS after adjuvant RT/CT was 2.1 vs 1.6 years for surgery alone, which was a significant difference The 2-years overall survival was 50 percent versus 39 percent, and 5-years was 28 percent versus 17 percent for patients receiving RT/CT versus surgery alone. Univariate and multivariate analysis revealed that adverse prognostic factors were positive lymph nodes (risk ratio [RR] 1.3) and high histologic grade (RR 1.2). T3 tumor status was found significant on univariate analysis only (RR 1.1). The authors concluded that the results from recent clinical trials support the use of adjuvant chemotherapy in resected pancreatic cancer. Results from the Mayo Clinic suggest improved outcomes after the administration of adjuvant radiochemotherapy after a complete resection of invasive pancreatic malignancies [559].

Treatment of recurrent disease

Chemoradiotherapy for the unresectable pancreatic cancer and biliary cancer has been used for improving survival. In one study, it was examined its safety and efficacy in cases with the

local recurrence of pancreatic or biliary cancer after primary resection. Seven consecutive patients with recurrence of carcinoma of pancreas (n=3) and biliary system (n =4) were treated chemoradiotherapy. Local recurrence occurred around the portal vein in 6 patients and remnant pancreas in one patient respectively. Disease free survival after primary surgery was 22 months (range: 5-84). All patients received 50 Gy of conformal three-dimensional radiotherapy with concurrent 5-FU, Gemcitabine or S-1. Grade 3 of anorexia and elevation of transaminase level occurred in one patient respectively. Local tumor response was observed in two patients of pancreatic and biliary cancer respectively. Median survival calculated from the start of the chemoradiotherapy was 15 months (range: 6-24) in pancreatic cancer and 14 months (range: 11-20) in biliary cancer [560].

Prognostic investigations
One study was conducted to assess changes in tumor vascularity using contrast-enhanced ultrasonography in patients with pancreatic carcinoma under systemic chemotherapy and to examine the correlation among vascular change, clinicopathologic factors, and outcome. Forty-one consecutive patients with histopathologically confirmed pancreatic carcinoma who had distant metastases and were under systemic chemotherapy were recruited. Contrast-enhanced ultrasonography was performed before and after 1 and 2 cycles of treatment. The vascular signals from the tumor were continuously recorded, and the highest signal intensity was selected and classified into 5 categories by their intensity. As for the tumor response determined by dynamic computed tomography after 2 cycles, 6 patients showed a partial response, 25 remained stable, and in 10 patients, the disease progressed. A significant relationship was observed between vascular change after 1 cycle and tumor response. Progression-free survival and overall survival were significantly short in the case of patients showing increased vascularity after 1 and 2 cycles of chemotherapy, compared with those who did not. It was concluded that contrast-enhanced ultrasonography was useful to evaluate tumor vascular changes and thereby the effect of systemic chemotherapy, as well as the prognosis of patients with advanced pancreatic carcinoma [561].

Radiotherapy (calculation)
To assess carbon ion beam dose variation due to bowel gas movement in pancreatic radiotherapy 10 pancreatic cancer inpatients were subject to diagnostic contrast-enhanced dynamic helical CT examination under breath-holding conditions, which included multiple-phase dynamic CT with arterial, venous, and delayed phases. The arterial-venous phase and arterial-delayed phase intervals were 35 and 145 s, respectively. A compensating bolus was designed to cover the target obtained at the arterial phase. Carbon ion dose distribution was calculated by applying the bolus to the CT data sets at the other two phases. Dose conformation to the clinical target volume was degraded by beam overshoot/undershoot due to bowel gas movement. The D95 for clinical target volume was degraded from 98 percent (range, 98.0-99.1 %) of the prescribed dose to 95 percent (range, 88.0-99.0 %) at 145 s. Excessive dosing to normal tissues varied among tissues and was, for example, 12.2 GyE/13.1 GyE (0 s/145 s) for the cord and 38.8 GyE/39.8 GyE (0 s/145 s) for the duodenum. The magnitude of beam overshoot/undershoot was particularly exacerbated from the anterior and left directions. It was concluded that bowel gas movement causes dosimetric variation to the target during treatment for radiotherapy. The effect of bowel gas movement varies with beam angle, with greatest influence on the anterior-posterior and left-right beams [562].

Radiotherapy (educational)
Before a multicentre trial of 3-D conformal radiotherapy to treat cancer of the pancreas, participating clinicians were asked to complete an accreditation exercise. This involved planning two test cases according to the study protocol, then returning hard copies of the plans and dosimetric data for review. Any radiation technique that achieved the specified constraints was allowed. Eighteen treatment plans were assessed. Seven plans were prescribed incorrect doses and two of the planning target volumes did not comply with protocol guidelines. All plans met predefined normal tissue dose constraints. The identified

errors were attributable to unforeseen ambiguities in protocol documentation. They were addressed by feedback and corresponding amendments to protocol documentation. Summary radiobiological measures including total weighted normal tissue equivalent uniform dose varied significantly between centres. This accreditation exercise successfully identified significant potential sources of protocol violations, which were then easily corrected. It was believed that this process should be applied to all clinical trials involving radiotherapy. Due to the limitations of data analysis with hard-copy information only, it is recommended that complete planning datasets from treatment-planning systems be collected through a digital submission process [563].

Novel agents

Pancreatic cancer is a particularly challenging malignancy, given its usually advanced stage at diagnosis and its rather limited treatment options. Gemcitabine has been standard therapy for advanced pancreatic cancer for well over a decade. The addition of capecitabine or erlotinib to gemcitabine has resulted in modestly improved, although still poor, overall survival. The majority of the recently completed randomized trials, however, have failed to demonstate an improvement of newer treatments over single-agent gemcitabine. Efforts currently underway center on new cytotoxic chemotherapy drugs, as well as novel targeted agents inhibiting various molecular pathways. Newly discovered proteins and cellular elements involved in tumor growth and invasion are potential therapeutic targets, and have become the focus of current trials, as well as future clinical trials. A better understanding of the biology of the disease at the basic science level, and epidemiology and risk factors from a public-health perspective, are needed [564].

Stem cell transplantation

Advanced unresectable pancreatic cancer has an extremely poor prognosis despite intensive chemotherapy. As a new therapeutic modality, it was investigated nonmyeloablative allogeneic hematopoietic stem cell transplantation from a related donor. Five patients with chemotherapy-resistant pancreatic cancer received allogeneic peripheral blood stem cell transplantation after a conditioning regimen consisting of low-dose total body irradiation and fludarabine. The prophylaxis for graft-versus-host disease consisted of mycophenolate mofetil and cyclosporine. The median age of the 5 patients was 54 years, and the median duration from diagnosis to nonmyeloablative allogeneic hematopoietic stem cell transplantation was 10 months. Three of the 5 patients achieved complete donor chimerism of peripheral T cells, at a median time of day 42. Acute graft-versus-host disease developed in 3 patients: grade 2 in 2 patients and grade 1 in 1. Tumor reduction was observed in 2 patients: 1 patient showed disappearance of the pancreatic tumor, and the other patient showed approximately 20 percent reduction of the tumor. Marked elevation of tumor necrosis factor-alpha was observed as the tumor regressed. It was concluded that lthough advanced pancreatic cancer progresses rapidly, some graft-versus-tumor effects and pivotal role of tumor necrosis factor-alpha were suggested [565].

Betulin

Betulin and betulinic acid are naturally occurring pentacyclic triterpenes showing cytotoxicity towards a number of cancer cell lines. These compounds can be found in the bark of the many plants. In one report it was compared the cytotoxic activity of crude birch bark extract and purified betulin and betulinic acid towards human gastric carcinoma (EPG85-257) and human pancreatic carcinoma (EPP85-181) drug-sensitive and drug-resistant (daunorubicin and mitoxantrone) cell lines. The results show significant differences in sensitivity between cell lines depending on the compound used, and suggest that both betulin and betulinic acid can be considered as a promising leads in the treatment of cancer [566].

Curcumin

Curcumin has been shown to inhibit the growth of various types of cancer cells; however, at concentrations much above the clinically achievable levels in humans. The concentration of curcumin achieved in the plasma after oral administration in humans was estimated to be around 1.8 microM. Now it was reported that treatment of BxPC-3 human pancreatic cancer cells with a low and single exposure of 2.5 microM curcumin for 24 h causes significant arrest of cells in the G2/M phase and induces significant apoptosis. Immunoblot studies revealed increased phosphorylation of H2A.X at Ser-139 and Chk1 at Ser-280 and a decrease in DNA polymerase-beta level in curcumin-treated cells. Phosphorylation of H2A.X and Chk1 proteins are an indicator of DNA damage whereas DNA polymerase-beta plays a role in the repair of DNA strand breaks. Normal immortalised human pancreatic ductal epithelial (HPDE-6) cells remained unaffected by curcumin treatment. In addition, we also observed a significant increase in the phosphorylation of Chk1 at Ser-345, Cdc25C at Ser-216 and a subtle increase in ATM phosphorylation at Ser-1981. Concomitant decrease in the expressions of cyclin B1 and Cdk1 were seen in curcumin-treated cells. Further, curcumin treatment caused significant cleavage of caspase-3 and PARP in BxPC-3 but not in HPDE-6 cells. Silencing ATM/Chk1 expression by transfecting BxPC-3 cells with ATM or Chk1-specific SiRNA blocked the phosphorylation of ATM, Chk1 and Cdc25C and protected the cells from curcumin-mediated G2/M arrest and apoptosis. The study reflects the critical role of ATM/Chk1 in curcumin-mediated G2/M cell cycle arrest and apoptosis in pancreatic cancer cells [567].

Aloe

The recent advances in the analysis of tumor immunobiology suggest the possibility of biologically manipulating the efficacy and toxicity of cancer chemotherapy by endogenous or exogenous immunomodulating substances. Aloe is one of the of the most important plants exhibiting anticancer activity and its antineoplastic property is due to at least three different mechanisms, based on antiproliferative, immunostimulatory and antioxidant effects. The antiproliferative action is determined by anthracenic and antraquinonic molecules, while the immunostimulating activity is mainly due to acemannan. A study was planned to include 240 patients with metastatic solid tumor who were randomized to receive chemotherapy with or without Aloe. According to tumor histotype and clinical status, lung cancer patients were treated with cisplatin and etoposide or weekly vinorelbine, colorectal cancer patients received oxaliplatin plus 5-fluorouracil (5-FU), gastric cancer patients were treated with weekly 5-FU and pancreatic cancer patients received weekly gemcitabine. Aloe was given orally at 10 ml thrice/daily. The percentage of both objective tumor regressions and disease control was significantly higher in patients concomitantly treated with Aloe than with chemotherapy alone, as well as the percent of 3-year survival patients [568].

Ginseng

Sprague-Dawley rats and ginseng from the roots of a 6-year-old fresh Panax ginseng C. A. Meyer plant were used in this study. Pancreatitis was induced by intraperitoneal injection of diethyldithiocarbamate for 4 weeks. Korean red ginseng was fed orally to rats for the next 3 weeks. At week 7, all rats were killed, and pancreatic tissues were analyzed. The results suggest that KRG has antioxidant therapeutic effects on superoxide dismutase inhibitor-induced pancreatitis by inhibition of nuclear factor kappaB [569].

MORE UNUSUAL TUMORS OF THE PANCREAS

Anaplastic carcinoma of the pancreas

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 [570].

Cystic pancreatic tumors

The diversity in the aggressiveness of cystic tumors of the pancreas – ranging from the usually benign serous cystadenoma to lesions of variable degrees of malignancy – was utilized for the identification of molecular factors that are involved in the occurrence of malignancy. It was analyzed the transcript profiles of different cystic tumor types. The results were confirmed at the protein level by immunohistochemistry. Also, functional studies with siRNA silencing were performed. Expression variations at the RNA and protein level were identified that are closely correlated with the degree of malignancy. Besides, all tumors could be classified effectively by this means. Many of the identified factors had not previously been known to be associated with malignant cystic lesions. siRNA silencing of the gene with the most prominent variation – the anti-apoptotic factor FASTK (Fas-activated serine/threonine kinase) – revealed a regulative effect on several genes known to be relevant to the development of tumors. It was concluded that by a molecular analysis of rare types of pancreatic cancer, which are less frequent in terms of disease, variations could be identified that could be critical for the regulation of malignancy and thus relevant to the treatment of also the majority of pancreatic tumors [571].

Early diagnosis of cancer in pancreatic cysts is important for timely referral to surgery. The aim of one study was to develop a predictive model for pancreatic cyst malignancy to improve patient selection for surgical resection. It was performed retrospective analyses of endoscopic ultrasound (EUS) and pathology databases identifying pancreatic cysts with available final pathological diagnoses. Main-duct intraductal papillary mucinous neoplasms (IPMNs) were excluded due to the clear indication for surgery. Patient demographics and symptoms, cyst morphology, and cyst fluid characteristics were studied as candidate risk factors for malignancy. 270 patients with pancreatic cysts were identified and analyzed (41 % men, mean age 62 years). Final pathological diagnoses were branch-duct IPMN (n=118, 50 % malignant), serous cystadenoma (n=71), pseudocyst (n=37), mucinous cyst adenoma/adenocarcinoma (n=36), islet cell tumor (n=4), simple cyst (n=3), and ductal adenocarcinoma with cystic degeneration (n=1). Optimal cut-off points for surgical resection were cyst fluid carcinoembryonic antigen (CEA) < 3,594 ng/ml, age >50, and cyst size >1.5 cm. Cyst malignancy was independently associated with weight loss (odds ratio 3.9), cyst

size >1.5 cm (odds ratio 2.4), and high CEA (odds ratio 5.3). In white patients >50 years old presenting with weight loss and cyst size >1.5 cm, the likelihood of malignancy was nearly sixfold greater than in those patients who had none of these factors (odds ratio 5.8, 95 % confidence interval 2.1 to 16.1). It was concluded that risk factors other than cyst size are important for determination of malignancy in pancreatic cysts. Exceptionally high cyst fluid CEA levels and certain patient-related factors may help to better predict cyst malignancy and the need for surgical treatment [572].

Neoplastic changes represent an important part of cystic deposits in pancreas. It is morphologically non-homogenous group of neoplasms with different occurrence depending on sex and age, different localization and different biologic properties. Together 13 patients with histologically proved cystic neoplasm of pancreas underwent surgery during the period of ten years from 1997 to 2007. They represent 6 percent of all patients operated for pancreatic tumor (213 patients). Women (9 patients) represented more than two thirds of all operated patients and deposits were more often localized in the head of pancreas (8). The most frequent operation was partial duodenopancreatectomy (7) and most frequently cystadenocarcinoma was identified histologically (5 times). Median survival of these patients is 54 months. Left sided resection, done in 5 cases, identified benign tumor in all patients; no recurrence was found in 2 years follow-up. It wasconcluded that cystic neoplasms localized in the pancreatic head are more frequent in men than in women and predominantly malignant, on the contrary localization in the tail of pancreas is particularly in younger women linked with benign tumor [573].

Cystic lesions of the pancreas are being recognized with increasing frequency and have become a more common finding in clinical practice because of the widespread use of advanced imaging modalities and the sharp drop in the mortality rate of pancreatic surgery. Consequently, in the past 2 decades, the nature of many cystic tumors in this organ has been better characterized, and significant developments have taken place in the classification and in our understanding of pancreatic cystic lesions. In contrast to solid tumors, most of which are invasive ductal adenocarcinomas with dismal prognosis, cystic lesions of the pancreas are often either benign or low-grade indolent neoplasia. However, those that are mucinous, namely, intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, constitute an important category because they have well-established malignant potential, representing an adenoma-carcinoma sequence. Those that are nonmucinous such as serous tumors, congenital cysts, lymphoepithelial cysts, and squamoid cyst of pancreatic ducts have no malignant potential. Only rare nonmucinous cystic tumors that occur as a result of degenerative/necrotic changes in otherwise solid neoplasia, such as cystic ductal adenocarcinomas, cystic pancreatic endocrine neoplasia, and solid-pseudopapillary neoplasm, are also malignant and have variable degrees of aggressiveness [574].

Intraductal papillary mucinous neoplasm (IPMN)

Intraductal papillary mucinous tumours (IPMT) were described as a distinct entity in I982. The extent of surgical resection for this disease remains controversial. Twelve patients with a diagnosis of IPMT were included in the present retrospective study. Ten out of twelve patients had symptoms suggesting chronic pancreatitis. Two patients were not operated on due to biopsy-verified metastases in the liver. Nine patients were treated with a total pancreatectomy and one with a pancreaticoduodenectomy. In the ten patients operated on for IPMT, histological examination showed eight non-invasive- and two invasive carcinomas. In six cases, multifocal extensive intraductal changes were found, affecting either most of or the whole pancreas. There was no perioperative mortality. Six patients were alive at follow-up without recurrence and four patients were dead, two of them with recurrence [575].

Growth rate

One study reported the growth rate in two cases of main duct pancreatic intraductal papillary-mucinous neoplasms (MD-IPMNs) demonstrating significant changes over several years' observation. The first patient was a 74-year-old woman with an incidental finding of diffuse dilatation of the main pancreatic duct (MPD). Endoscopic retrograde pancreatography (ERP) identified a 5 mm filling defect. Three years later computed tomography (CT) revealed a 20 mm mass occupying the MPD. The second patient was a 67-year-old woman who presented with back pain. Abdominal CT revealed a 5 mm mass in the dilated MPD. Five years later, CT and ERP showed a 20 mm mass occupying the markedly dilated MPD. Both patients subsequently underwent pancreatectomy. Histologically, the tumors showed an intraductal papillary growth occupying the dilated main pancreatic duct and comprised of mucin-containing columnar epithelial cells. The tumor volume doubling time of these MD-IPMNs was 141 and 304 days in patient 1 and 2, respectively, with a mean of 223 days. The present reports demonstrate the ability of benign MD-IPMNs to grow at a significant rate, supporting the current consensus guidelines that MD-IPMNs require surgical resection [576].

Ways of detection

To define how patients with pancreatic cysts are being diagnosed and treated 401 patients were evaluated between 2004 and 2007. Pancreatic cysts were incidentally discovered in 71 percent (284 of 401) of patients. There was no statistically significant difference in age (60 vs 63 years), cyst size (31 vs 27 mm), or histological diagnosis between symptomatic patients and patients with incidentally discovered cysts. Whereas the majority of symptomatic patients had their cystic neoplasms resected on diagnosis, 50 percent (142 of 284) of incidentally discovered cysts were initially managed nonoperatively. Of the patients who were managed with surveillance, 13 (8 %) subsequently underwent resection after a median of 2.1 years because of an increase in cyst size, development of symptoms, increasing tumor markers, worrisome endoscopic ultrasonography findings, or patient anxiety. The most common diagnosis among resected lesions was either main-duct intraductal papillary mucinous neoplasm (25 %) or branch-duct intraductal papillary mucinous neoplasm (23 %). Invasive cancer was found in 29 of 256 (11 %) resected cystic neoplasms, 9 of which were incidentally discovered, and in 7 percent (1 of 13) of patients who underwent watchful waiting prior to resection. Incidentally discovered pancreatic cystic neoplasms composed 71 percent of our series, of which 50 percent were immediately resected. Subsequent morphologic changes or development of symptoms prompted an operation in 8 percent of patients after a period of surveillance. Invasive malignancy was present in 11 percent of all resected specimens but in 38 percent of main-duct intraductal papillary mucinous neoplasms [577].

Intraductal papillary mucinous neoplasms have gained recognition in recent years as premalignant precursors to pancreatic cancer that enable early detection and often are found incidentally at imaging. Accurate diagnosis and optimal, finely tuned management of these lesions are important and require collaboration across various disciplines, including radiology, endoscopy, surgery, and pathology. Several imaging modalities can visualize these lesions adequately, each with specific advantages and disadvantages. Multidetector computed tomography and magnetic resonance cholangiopancreatography are generally the first-line imaging modalities; endoscopic imaging such as endoscopic ultrasound and endoscopic retrograde cholangiopancreatography are beneficial when the former 2 modalities are equivocal. Surgical candidates generally include patients with main duct lesions or branch duct lesions greater than 3 cm or any possessing a solid component. A management algorithm indicating when surgery should be pursued was proposed. For nonsurgical and postsurgical patients, follow-up management is important to monitor growth and recurrence, and risks from repeated radiation exposure should be taken into account. Furthermore, issues of multifocality and increased predisposition of the pancreas to ductal

adenocarcinoma must be addressed at follow-up evaluation. A follow-up management algorithm also was also proposed in the review [578]

Risk of cancer

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 vital statistics. 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 patients with BD-IPMNs are at a high risk for pancreatic adenocarcinomas. During the follow-up, careful examination is required to detect the development of PDAs in patients with BD-IPMNs [579].

The biologic and clinical behavior of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) and IPMN-associated adenocarcinomas is different from ductal pancreatic cancer in having a less aggressive tumor growth and significantly improved survival. Up to date, the molecular mechanisms underlying the clinical behavior of IPMNs are incompletely understood. Now 128 cystic pancreatic lesions were prospectively identified during the course of 2 years. From the corresponding surgical specimens, 57 IPMNs were separated and subdivided by histologic criteria into those with low-grade dysplasia, moderate dysplasia, high-grade dysplasia, and invasive cancer. Twenty specimens were suitable for DNA isolation and subsequent performance of array CGH. While none of the IPMNs with low-grade dysplasia displayed detectable chromosomal aberrations, IPMNs with moderate and high-grade dysplasia showed frequent copy number alterations. Commonly lost regions were located on chromosome 5q, 6q, 10q, 11q, 13q, 18q, and 22q. The incidence of loss of chromosome 5q, 6q, and 11q was significantly higher in IPMNs with high-grade dysplasia or invasion compared with PDAC. Ten of 13 IPMNs with moderate dysplasia or malignancy had loss of part or all of chromosome 6q, with a minimal deleted region between linear positions 78.0 and 130.0. This study is the first to use array CGH to characterize IPMNs. Recurrent cytogenetic alterations were identified and were different than those described in PDAC. Array CGH may help distinguish between these 2 entities and give insight into the differences in their biology and prognosis [580].

A 52-year-old man with a history of distal gastrectomy for gastric cancer was admitted because of jaundice. CT scan revealed double tumors in the pancreatic head and body concomitant with multicystic lesions of the pancreas. Total pancreatectomy with splenectomy and remnant gastrectomy was performed. Final histological diagnosis was double invasive ductal carcinomas of the pancreas head and tail with multifocal branch duct intraductal papillary mucinous adenomas of the pancreas. The present case suggests that entire pancreas might have malignant potential in patients with intraductal papillary mucinous neoplasms [581].

A consensus conference has recommended close observation of branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) smaller than 30 mm, without symptoms or mural nodules. One study investigated whether these recommendations could be validated in a

single-centre experience of BD-IPMNs. Some 190 patients with radiological imaging or histological findings consistent with BD-IPMN were enrolled between 1998 and 2005. Those with less than 6 months' follow-up and no histological confirmation were excluded. BD-IPMN was diagnosed by computed tomography and pancreatography in 105 patients and pathologically in 85. Eighteen patients had adenoma, 53 borderline malignancy, five carcinoma in situ and nine invasive carcinoma. Findings associated with malignancy were the presence of radiologically suspicious features and a cyst size of at least 30 mm. Had consensus guidelines been applied, 54 patients would have undergone pancreatic resection, whereas only 28 of these patients actually had a resection; 12 of the latter patients had a malignancy compared with none of the 26 patients who were treated conservatively. It was concluded that a simple increase in cyst size is not a reliable predictor of malignancy. Observation is recommended for patients with a BD-IPMN smaller than 30 mm showing no suspicious features on imaging [582].

Intraductal papillary mucinous neoplasm (IPMN) was first described by Ohashi et al as "mucin-producing cancer" that affected the main pancreatic duct and produced excessive quantities of mucus, which filled and distended the ductal system. Prediction of malignancy of IPMN is important not only for indication of operation but for selection of operative procedure. International Consensus Guidelines recommended to resect all main duct and mixed variant IPMNs, and also recommended to resect branch duct IPMNs with symptoms. However, the criteria for resection in the branch duct IPMNs are still unclear. One study aimed to determine the predictive factors for malignancy in IPMN, particularly cancer invasion in IPMNs. It was reviewed 26 cases with IPMN operated from 2003 to 2007. Among them, 21 cases were branched type, and the others were main duct type. It was measured diameter of main pancreatic duct, cystic lesion size and intramural nodule size by endoscopic ultrasonography or computed tomography and serum levels of CEA and CA19-9. As for factors to predict malignancy only in branched type, the intramural nodules size and was significantly larger in the cases with cancer than that in the cases without cancer. The analysis all types IPMNs showed significant difference in the main duct diameter between 15 benign and 11 malignant cases (5.5 $\pm$ 4.0 mm vs 10.9 $\pm$ 4.5 mm). Moreover, among the 11 cases whose diameter of main pancreatic duct was less than 7 mm, no malignancy was detected. These results suggest that the diameter of main pancreatic duct as well as intramural nodules size is useful for prediction of malignancy and that minimally-invasive surgery such as spleen-preserving distal pancreatectomy can be safely indicated for the cases whose diameter of main pancreatic duct is less than 7 mm [583].

It was investigated preoperative findings that are useful to distinguish intraductal papillary-mucinous neoplasm (IPMN) subtypes. One hundred twenty-three patients who underwent pancreatectomy for IPMN were analyzed clinicopathologically and radiologically. Invasive IPM carcinomas (IPMCs) were subdivided into early-stage nonaggressive (minimally invasive IPMC [MI-IPMC]) and more advanced and aggressive (invasive carcinoma originating in IPMC [IC-IPMC]) subtypes according to recently proposed pathological criteria. The lesions consisted of 27 IPMNs with low-grade dysplasia, 14 IPMNs with moderate dysplasia, 21 IPMNs with high-grade dysplasia, 30 MI-IPMCs, and 31 IC-IPMCs. Multidetector-row computed tomography detected a component of invasive carcinoma in IC-IPMC with 86 percent sensitivity and 100 percent specificity. In patients with IPMNs other than IC-IPMC, multivariate analysis demonstrated 3 significant predictive factors of malignancy: IPMN size (>40 mm), IPMN duct type (main pancreatic duct or mixed type), and the presence of a mural nodule or thick septum. The diagnostic score obtained using these 3 factors showed a strong correlation with the presence of malignancy. It was concluded that regarded preoperative evaluation of patients with IPMN, it is recommended to rule out IC-IPMC using multidetector-row computed tomography and then to categorize IPMN other than IC-IPMC according to malignant potential based on the diagnostic score [584].

Molecular biology

CD44v6

The purpose of thone is 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). 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. These data indicate that CD44v6 expression determines the morphology and aggressiveness of IPMNs and is involved in development and invasion of IPMNs [585].

CD133

The rate of intraductal papillary mucinous neoplasm (IPMN) progression is much slower than that of invasive ductal adenocarcinomas. The identification of a clinicopathological marker to distinguish IPMNs from ductal adenocarcinomas is important for understanding the molecular mechanisms of pancreatic cancer. It was examined the expression pattern of the cell surface marker CD133, which has been used to identify putative cancer stem cells from solid tumors, in adult pancreatic ductal adenocarcinomas (n=10) and IPMNs (n=34). CD133 expression was detected in the centroacinar region and intralobular ductal cells of normal pancreas. CD133 expression was also observed in ductal adenocarcinomas. In contrast, CD133 expression was not observed in the mucin-producing epithelial cells and carcinoma cells on IPMNs. These results demonstrate that the expression of CD133 is down-regulated in IPMNs, suggesting that loss of CD133 expression might be a useful clinicopathological marker distinguishing IPMNs from ductal adenocarcinomas [586].

KOC

To evaluate if immunocytochemical expression of K homology domain containing protein overexpresssed in cancer (KOC) in biliary brushings and fine needle aspiration improves the diagnostic capability of cytology for intraductal papillary mucinous neoplasm (IPMN) and pancreatic ductal adenocarcinoma 14 pancreatic cancers, 15 IPMNs and 7 chronic pancreatitis cases were investigated. The cytology smears and surgical specimens were stained with antibody to KOC (1:500). The intensity (scale 0-3+) and percentage of cells staining were evaluated in pathologic lesions, and diffuse (>75 % of cells) staining of 3+ intensity was considered positive. There was 100 percent specificity for diagnosing pancreatic cancer. The sensitivity was greater in histology (79 %) than cytology (71 %). All chronic pancreatitis and IPMN cases, including IPMN with high grade dysplasia, were negative. Benign epithelium adjacent to pancreatic cancer or IPMN was also negative. This study demonstrated that pancreatic adenocarcinoma can be differentiated from IPMN and benign ductal epithelium using KOC expression. This could be useful in cytologic cases where atypical features preclude a definitive diagnosis of malignancy [587].

WWOX

It has previously been shown that WW domain-containing oxidoreductase (WWOX) has tumour-suppressing effects and that its expression is frequently reduced in pancreatic carcinoma. In one study, it was examined WWOX expression in intraductal papillary mucinous neoplasm of the pancreas (IPMN) to assess the function of WWOX in pancreatic

duct tumourigenesis using immunohistochemistry and methylation-specific polymerase chain reaction analysis. Among 41 IPMNs including intraductal papillary mucinous adenomas and intraductal papillary mucinous carcinomas, loss or reduced WWOX immunoreactivity was detected in 3 (15 %) of 20 IPMAs and 17 (81 %) of 21 IPMCs. In addition, hypermethylation of the WWOX regulatory site was detected in 1 (33 %) of 3 WWOX(-) IPMAs and 9 (53 %) of 17 WWOX(-) IPMCs, suggesting that hypermethylation may possibly be important in the suppression of WWOX expression. Reduction of WWOX expression was significantly correlated with a higher Ki-67 labelling index but was not correlated with the ssDNA apoptotic body index. Interestingly, decreased WWOX expression was significantly correlated with loss of SMAD4 expression in these IPMNs. The results indicate that downregulation of WWOX expression by the WWOX regulatory region hypermethylation is critical for transformation of pancreatic duct [588].

Imaging

To retrospectively evaluate the usefulness of multidetector computed tomography (MDCT) with multiplanar reformations (MPRs) and curved planar reformations (CPRs) for detecting protruding lesions in intraductal papillary mucinous neoplasms of the pancreas (IPMNs) as compared with single-detector CT (SDCT) and endoscopic ultrasonography (EUS) 86 patients with IPMNs were imaged either with SDCT (n=52) or MDCT with MPRs/CPRs and EUS (n=34). The diagnostic accuracy of each imaging modality for identifying protruding lesions was compared with histological samples. Among the patients in whom protruding lesions were histopathologically identified, the lesions were detected in 9 of the 33 patients subjected to SDCT (52 % accuracy), in 17 of the 25 patients subjected to MDCT with MPRs and CPRs (77 % accuracy), and in 21 of the 25 patients subjected to EUS (71 % accuracy). Thus, significant difference was observed between MDCT and SDCT regarding accuracy; however, no significant difference was seen between MDCT and EUS. Protruding lesions of less than 10 mm in height were significantly better visualized with MDCT (53 %) than with SDCT (13 %) [589].

CT

A retrospective study evaluated the suitability of computed tomography (CT) to detect malignancy while following patients with branch-type IPMN, most of which are benign and may be treated with observation alone was performed. Forty-two surgical specimens resected from patients with a diagnosis of branch-type IPMN were pathologically classified as benign (n=26), which included hyperplasia and adenoma, or malignant (n=16), including moderate dysplasia or adenocarcinoma. It was compared the differences in the sizes of the tumor and main pancreatic duct (MPD) and the presence of mural nodules on CT between the groups. In the malignant group, it was observed a significantly larger tumor size (48 vs 24 mm) and significantly increased dilation of the MPD (9.3 vs 5.0 mm) than those seen in the benign group. The accuracy of CT diagnosis of mural nodules, however, was only 62 percent. A tumor diameter > 40 mm or an MPD diameter >10 mm predicted malignancy with a sensitivity and negative predictive value of 94 and 96 percent, respectively. It was concluded that either tumor size or MPD dilation detected by CT could predict the majority of malignant branch-type IPMNs. Increases in these morphological characteristics on CT images during the follow-up period would be an accurate method to predict a diagnosis of malignancy [590].

MRI

The purpose of this study was to compare 2-dimensional (2D) and 3D magnetic resonance cholangiopancreatography (MRCP) for image quality and diagnostic performance in the evaluation of pathologically verified intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Twenty-one patients (14 women and 7 men; mean age, 69 years; range, 43-93 years) who underwent 2D and 3D MRCPs on a 1.5-T system for pathologically confirmed

IPMN were studied. Two-dimensional MRCP protocol included multiplanar thin- and thick-slab single-shot fast spin-echo imaging, coronal single-shot fast spin-echo, and transverse T2-weighted fast spin-echo imaging. Three-dimensional MRCP was performed using a fast-recovery fast spin-echo sequence with single-volume acquisition and maximum intensity projection reconstructions. Using a 5-point scale, 2 readers independently evaluated MRCPs for image quality, visualization of the pancreatic duct, and visualization of the cystic lesions. Intraductal papillary mucinous neoplasm's morphological features (septa, mural nodules, and duct communication) were also graded similarly to predict benignity or malignancy. A pancreatic surgeon reviewed the 21 MRCPs to determine the usefulness of 3D MRCP compared with that of 2D MRCP for surgical planning. Of the 21 IPMNs, 11 were side-branch IPMNs and 10 were main-duct-lesions IPMNs with side-branch involvement. A statistically significant improvement in image quality and visualization of the PD and cystic lesion was demonstrated with 3D MRCP in comparison with that demonstrated with 2D MRCP. The morphological details of IPMN were also identified, with higher confidence with 3D MRCP in comparison with that using 2D MRCP. Two-dimensional and 3D MRCPs performed similarly for predicting benign and malignant lesions, with sensitivity ranging from 50 to 67 percent and specificity ranging from 87 to 93 percent. The pancreatic surgeon preferred 3D to 2D MRCP for surgical evaluation and planning in 14 of 21 cases. It was thus concluded that compared with 2D MRCP, 3D MRCP provides better image quality, offers superior evaluation of the pancreatic duct and morphological details of IPMN, and is preferred for surgical planning [591].

EUS

Because of greater recognition and improved imaging capabilities, intraductal papillary mucinous neoplasms (IPMNs) are being diagnosed with increasing frequency. IPMNs of the main pancreatic duct cause symptoms and lead to pancreatitis. Side-branch IPMNs are thought to cause symptoms less frequently, and their association with pancreatitis is not well defined. A total of 305 patients underwent EUS examinations between 2002 and 2006 for pancreatic cystic lesions. The main outcome measure was the frequency of acute or chronic pancreatitis that was not procedurally related. Thirty-two patients had side-branch IPMNs, and 11 (34 %) had pancreatitis. Three patients reported a single episode, and 8 patients reported having recurrent episodes of pancreatitis. Overall, 17 (53 %) patients had symptoms possibly attributable to side-branch IPMN. Female sex (73 % vs 38 %) and multiple pancreatic lesions (54 % vs 24 %) were more commonly seen in those with pancreatitis, but were not statistically significant factors. Larger cyst size or cyst fluid marker levels did not appear associated with pancreatitis occurrence. EUS-FNA demonstrated communication with the pancreatic duct in 94 percent and thick, mucinous fluid in 84 percent. It was concluded that pancreatitis was frequently associated with the presence of side-branch IPMNs in our referral practice. Side-branch IPMNs should be considered in the differential diagnosis of patients with recurrent pancreatitis with cystic lesions seen on imaging studies. EUS-FNA was the most useful modality in helping to differentiate side-branch IPMNs from other lesions [592].

Differential diagnoses

Cystic and neuroendocrine pancreatic neoplasms are quite rare tumors which diagnosis is often difficult due to their non specific symptomatology and limited diagnostic accuracy of conventional diagnostic instruments. A young woman was now admitted with abdominal pain and dyspepsia. Instrumental diagnosis revealed a cystic pancreatic lesion which seems to be malignant as CEA of pancreatic liquid was increased. The patient underwent distal spleno-pancreatectomy and postoperative histological examination found IPMN associated with MCN and furthermore there was occasional diagnosis of a small neuroendocrine tumor in the pancreatic tail. Radical surgical treatment is indicated in many cases of main duct IPMN and in case of MCN with signs of malignant transformation. Surgical treatment is also the gold standard for pancreatic neuroendocrine tumors if they are singular and in M0 stage [593].

Extrapancreatic tumors

The purpose of one study was to evaluate the incidence and clinicopathological features of extrapancreatic tumors associated with IPMN. Thirty-seven patients with IPMN of the pancreas, confirmed by surgical resection and typical findings of endoscopic ultrasonography and CT imaging between 1998 and 2006 were included. Seventeen patients were diagnosed with surgical resection and biopsy, and others by typical imaging findings of IPMN. These patients were examined for the development of extrapancreatic tumors. Of 37 patients with IPMN, 14 (38 %) had 18 extrapancreatic tumors, and 10 (27 %) had 13 extrapancreatic malignancies. Five, six, and two extrapancreatic malignancies had been diagnosed before, during, and after the diagnosis of IPMN. Gastric adenocarcinoma (3 patients) and colorectal carcinoma (3 patients) were the most common neoplasms. Other extrapancreatic tumors included lung cancer (n=2), prostatic cancer (n=1), renal cell carcinoma (n=1), cholangiocellular carcinoma (n=1), urinary bladder cancer (n=1), and gallbladder cancer (n=1), respectively. As benign tumor, there were two gallbladder adenoma, one gastric adenoma, one colonic adenoma and one benign ovarian cystic neoplasm, respectively. It was concluded that IPMN is associated with high incidence of extrapancreatic tumors, particularly gastric and colorectal neoplasms. Upper gastrointestinal endoscopy and colonoscopy should be done, and systemic surveillance for the possible occurrence of other tumors may allow early detection of extrapancreatic tumor in patients with IPMN [594].

Predictive factors

Noninvasive intraductal papillary mucinous neoplasms (IPMNs) have a favorable prognosis; however, the prognosis of invasive intraductal papillary mucinous carcinoma (invasive IPMC) is poor. Identification of predictive factors for differentiating IPMC from benign IPMNs would assist in providing appropriate treatment. In a retrospective study (1999-2006) 54 patients with IPMN who underwent surgery; histologic examination showed benign adenomas in 29, carcinoma in situ in 14, and invasive carcinoma in 11 patients. Age of 70 years or older, presence of mural nodules, mural nodule size of 5 mm or larger, and carcinoembryonic antigen (CEA) level in pancreatic juice of 110 ng/mL or higher (as obtained by preoperative endoscopic retrograde pancreatography) were predictive of a malignant IPMN by univariate analysis, and a CEA level of 110 ng/mL or higher in pancreatic juice was identified as the only independent predictive factor for the malignant entity. The presence of jaundice or body weight loss, main pancreatic duct type, presence of mural nodules, mural nodule size of 5 mm or larger, and CEA level in the pancreatic juice of 110 ng/mL or higher were all predictive of invasive IPMCs by univariate analysis. The authors concluded that measurement of the CEA level in pancreatic juice should be considered in the diagnosis of IPMC [595].

In immune suppressed patients

In immunosuppressed patients with branch duct intraductal papillary mucinous neoplasm (IPMN-Br) associated with solid organ transplantation, the risk of major pancreatic surgery has to be weighed against the risk of progression to malignancy. Recent studies show that IPMN-Br without consensus indications for resection can be followed conservatively. It was compared clinical and imaging data at diagnosis and follow-up of 33 IPMN-Br patients with solid organ transplant (T-IPMN-Br) with those of 57 IPMN-Br patients who did not undergo transplantation (NT-IPMN-Br). In T-IPMN-Br, it was noted pre- and post-transplant imaging and cyst characteristics. T-IPMN-Br patients were significantly younger than the NT-IPMN-Br patients (63 vs 68 years). The median duration of follow-up for the groups was similar (29 vs 28 months). Consensus indications for resection were present in 24 percent (8/33) of T-IPMN-Br patients and 32 percent (18/57) of NT-IPMN-Br. New consensus indications for resection were noted in 6 percent (2/33) of patients in the T-IPMN-Br group during a median follow-up of 17 months (range, 3-100 months) compared with 4 percent (2/57) of patients in

the NT-IPMN-Br group. Eleven patients (10 NT-IPMN-Br, 1 T-IPMN-Br) underwent surgery during follow-up. Only one NT-IPMN-Br patient was diagnosed with malignancy; all others had benign IPMN-Br. It was concluded that in participants with IPMN-Br, short-term follow-up after solid organ transplant was not associated with any significant change in cyst characteristics suggesting that incidental IPMN-Br, even in the setting of immunosuppression post-transplant, can be followed conservatively [596].

Frozen section at operation

The clinical significance of a positive intraoperative frozen section analysis of the pancreatic margin, especially for adenoma or borderline lesion, is not well understood during operations for intraductal papillary mucinous neoplasm of the pancreas. Data from 130 consecutive patients who underwent intraductal papillary mucinous neoplasm resection in a single institution were therefore retrospectively analyzed. In the first intraoperative frozen section analysis, 26 patients were positive for adenoma or borderline lesion, 10 for carcinoma in situ, 2 for cancer cells floating in the duct, and 6 for invasive cancer. Twenty-nine patients underwent additional resection, and 105 patients finally achieved a negative pancreatic margin. Among 18 patients with a positive pancreatic margin for adenoma or borderline lesion, only 1 had a recurrence. All 20 patients who suffered a recurrence harbored invasive intraductal papillary mucinous carcinoma in resected specimens. In multivariate analysis, predictive factors of recurrence after intraductal papillary mucinous carcinoma resection were the presence of lymph node metastasis, serosal invasion, and a high level of serum carbohydrate antigen 19-9. The presence of adenoma or borderline lesion at the pancreatic margin does not always warrant further resection because of the low recurrence rate in the remnant pancreas. Recurrence after intraductal papillary mucinous neoplasm resection is influenced primarily by the presence and extent of invasive cancer rather than the status of the pancreatic margin [597].

Hemodialysis

Pancreatic cystic lesions are not necessarily rare, and it is important to diagnose whether pancreatic cystic lesions are neoplastic such as intraductal papillary mucinous neoplasm (IPMN) because of its malignant potential. Reports on pancreatic cystic lesions in hemodialysis patients are limited. The aim of one study was to clarify the prevalence and characteristics of pancreatic cystic lesions in hemodialysis patients. It was reviewed 1012 consecutive hemodialysis patients and 11,100 patients (controls) without renal disease who underwent transabdominal ultrasonography between 2003 and 2005. Patients' sex ratio (female-to-male) was less, and the age was older in hemodialysis patients. The prevalence both of pancreatic cystic lesions and IPMNs was significantly higher in hemodialysis patients than in controls (9.3 % vs 1.3 % and 2.8 % vs 0.2 %). The incidence of IPMNs in hemodialysis patients with pancreatic cystic lesions was higher than that in controls with pancreatic cystic lesions (30 % vs 17 %). Multivariate logistic regression analysis revealed that the odds ratios of pancreatic cystic lesions and IPMNs were 6.4 and 9.3 in hemodialysis patients compared with controls [598].

Serous cystadenomas

With more widespread use of imaging, cystic neoplasms of the pancreas are being diagnosed with increased frequency. Serous cystadenomas are the most common type of cystic neoplasm of the pancreas and have a natural history and malignant potential different than that of other cystic neoplasms. Although characteristic findings on imaging may be supportive, definitive diagnosis of these lesions often cannot be made by imaging alone. Endoscopic ultrasound with fine needle aspiration and cyst aspiration may facilitate the

diagnosis, and after definitive diagnosis, patients with lesions that are small and asymptomatic may be followed with serial imaging. If definitive diagnosis cannot be made or if the patient is symptomatic, resection is warranted. In addition, large (> 4 cm) serous cystadenomas should be resected in appropriate surgical candidates given their propensity for growth and developing symptoms [599].

Many patients with benign serous cystadenoma (SCA) of the pancreas will undergo resection because of the inability to reliably discriminate between SCA and premalignant mucinous cysts (intraductal papillary mucinous neoplasm – IPMN – mucinous cystic neoplasm – MCN]). Cyst fluid from patients with SCA (n=15), non main-duct and noninvasive IPMN (n=32), and noninvasive MCN (n=12) was aspirated at the time of operative resection and analyzed. Commercially available and custom designed multiplex assays (Luminex) were performed using a biomarker panel developed for pancreatic cancer. Differential protein expression (fluorescence intensity, FI) was compared between the 3 groups for each protein. Unsupervised sample clustering (hierarchical clustering) and supervised sample classification (prediction analysis for microarrays – PAM) was then performed. Significant differential protein expression was identified between SCA and IPMN (34/51 proteins, 67 %) and between SCA and MCN (13/51 proteins, 25 %). The majority of proteins were down-regulated in IPMN and MCN compared with SCA. The only proteins significantly overexpressed in the cyst fluid of patients with mucinous cysts were CEA (median FI: IPMN 11.4, MCN 13.0, SCA 5.3) and CA72.4 (median FI: IPMN 10.4, MCN 10.5, SCA 9.9). Unsupervised cluster analysis demonstrated distinct clustering of SCA and IPMN with some cross-over between MCN. Supervised sample classification with 14 proteins had an overall accuracy rate of 92 percent between SCA and IPMN. In this study differential cyst fluid protein expression was observed between SCA and IPMN for the majority of proteins assessed and multimarker sample classification accurately discriminated between SCA and IPMN in 92 percent of patients [600].

Diffuse serous cystadenomas of the pancreas are extremely rare, with only 8 cases reported previously, and have been associated with neuroendocrine tumors in only two patients. Some have been seen in von Hippel-Lindau disease. The management of these tumors poses a challenge due to their rarity and uncertain malignant potential. It was reported a case of diffuse serous cystadenoma associated with neuroendocrine carcinoma in a 35-year-old woman. A 35-year-old woman with mild abdominal pain was diagnosed as having a cystic pancreatic mass on ultrasonography. On contrast-enhanced CT scan, MRI and MRCP imaging, a spongy lesion was found to replace the entire pancreas, and was diagnosed as diffuse serous cystadenoma. Serum biochemistry for amylase, lipase, CA 19-9 and CEA was normal. Screening for retinal and CNS lesions was also unremarkable. A total pancreatectomy was performed, and the patient recovered well. Histopathological examination of the specimen revealed microcysts and macrocysts replacing the entire pancreas, the largest being 3.5 cm. The cysts were lined with a single layer of cuboidal to flattened cells. An endocrine tumor abutting the cystic component was found, having neoplastic cells in a trabecular pattern. Metastasis of the neuroendocrine component was seen in the adherent lymph nodes. A diagnosis of diffuse serous cystadenoma associated with neuroendocrine carcinoma was made. It was concluded that diffuse serous cystadenomas of the pancreas are extremely rare tumors. In young patients, they may harbour associated malignancy, and may be the first presentation of von Hippel-Lindau disease. Aggressive surgical resection with long-term follow-up may be worthwhile in this group of patients [601].

Serous microcystic adenoma

The diagnosis of serous microcystic adenoma (SMA) is usually straightforward. For small biopsies and/or unusual variants, the differential diagnosis includes other pancreatic or

metastatic neoplasms showing cystic or clear cell features. It was therefore evaluated immunostains for potential use in the diagnosis of SMA. Cases of SMA were identified from archival files. Tissue cores (2 per block) were arrayed to create a microarray of cores measuring 2 mm each. Additionally, microarrays previously constructed from 56 pancreatic adenocarcinomas and 64 pancreatic endocrine tumors (PENs) were studied. The microarrays were stained with calponin, chromogranin, CD10, alpha-inhibin, and monoclonal neuron-specific enolase (m-NSE). Subsequently, some were stained with MUC6, melan-A, D2-40, h-caldesmon, smooth muscle actin, and smooth muscle myosin. For SMAs, staining was seen with calponin (85 %), alpha-inhibin (96 %), and m-NSE (96 %). Focal weak staining was seen with MUC6 (65%). All SMAs were negative with chromogranin, CD10, melan-A, D2-40, h-caldesmon, smooth muscle actin, and smooth muscle myosin. In contrast, calponin was negative in all pancreatic cancers and PENs. Staining for alpha-inhibin was absent in pancreatic cancers and present in 4 percent of PENs; whereas immunoreactivity for m-NSE was present in 27 percent of pancreatic cancers and 74 percent of PENs. Chromogranin staining was present in 9 percent of pancreatic cancers and 100 percent of PENs. An immunohistochemical profile of staining with calponin, alpha-inhibin, and m-NSE and absent staining with chromogranin supports the diagnosis of SMA, and distinguishes SMA from pancreatic cancers and pancreatic endokrine tumors. Calponin and alpha-inhibin are the most useful positive markers for serous microcystic adenoma, and are negative in most entities in the differential diagnosis [602].

Serous microcystic adenoma with oncocytic change
It was reported a case of pancreatic serous microcystic adenoma with extensive oncocytic change in a 73-year-old woman. Histologically the tumor consisted of numerous small cysts, separated by thin or broad fibrous septa. These cysts were lined with uniform cells having abundant eosinophilic granular cytoplasm, which was negatively or weakly stained with PAS. Immunohistochemically, the cyst-lining cells were positive for cytokeratin (CK) 7, CK19, MUC1, MUC6, alpha-inhibin, and neuron-specific enolase (NSE), and negative for CK8, CK20, MUC2, and MUC5AC; these immunoprofiles coincide with those of serous microcystic adenoma. Immunostaining with anti-mitochondrial antibody showed dense granular positivity in the cytoplasm, which suggested an oncocytic phenotype. Thus, the case was considered a variant of serous microcystic adenoma characterized by extensive oncocytic change. It may pose problems in the differential diagnosis of the cystic pancreatic tumors with oncocytic change, but can be diagnosed on histology and immunohistochemistry [603].

Mucinous adenoma

A 60-year-old woman was referred for evaluation of a cystic mass in the pancreatic body that extended to the tail. Transabdominal ultrasonography demonstrated an oval cystic mass 24 cm in diameter, filled with debris. On the cyst wall there was a wide-based, smooth-surfaced, heterogeneous high-echoic protrusion that was 5 cm in diameter. On CT the protrusion showed internal enhancement. Endoscopic pancreatography showed no intraductal mucin or communication with the cyst. A distal pancreatectomy was performed under the diagnosis of mucinous cystadenocarcinoma. Grossly there was a brownish, hemispherical protrusion into the thin monolocular cyst. The cut surface of the protrusion showed a peripheral yellow-brownish area and an internal wine-colored area. Histopathologically the cyst wall consisted of tall columnar cells without atypical nuclei, ovarian-type stroma beneath the epithelium, and fibrotic tissue with abundant capillary vessels, suggestive of a mucinous cystadenoma. The protrusion was composed of peripheral organized hematoma without a covering epithelium, and internal hemorrhage and many capillary vessels, with no evidence of tumor cell necrosis. These histopathological findings appear to be similar to those of chronic expanding hematoma. The formation of a huge mural hematoma in a mucinous cystic neoplasm can occur as a repair process after the breaking of intrawall vessels [604].

Solid and pseudopapillary tumor (Frantz's tumor)

Solid and pseudopapillary tumor (Frantz's tumor) is a rare low-grade neoplasm of the pancreas. It was reported six new cases. A retrospective review was considered on six Tunisan patients who had solid and pseudopapillary tumor of the pancreas. A review of medical registries and morphological analysis with immunohistochemical study were carried out in all cases. Four patients were female and two patients were male with a median age of 28 years (range: 14-68 years). Abdominal pain was the most common initial symptoms (5/6 cases). Abdominal computed tomography and/or ultrasonography was used in all the cases. The tumour was in the tail of the pancreas in 4 patients and in the body of the pancreas in one patient; one tumor involved all the pancreas. The median diameter of the tumor was 17 cm (range: 8-35 cm). Three tumors had an extrapancreatic extension. All patients underwent surgical resection. No adjuvant therapy was recommended. The mean follow up period was 24 months (range: 5-78 months). Only one patient died during the surgery. Except for this patient, none experienced tumor recurrence or tumor-related mortality during the follow up period. Solid and pseudopapillary tumour of the pancreas is an uncommon neoplasm which shows distinct clinicopathologically characteristics. Despite diverse studies, its histogenesis remains undetermined. This tumor should be distinguished from other pancreatic neoplasms because its prognosis is excellent after surgical resection [605].

Solid-pseudopapillary neoplasms (SPNs) are rare pancreatic tumors with malignant potential. Longterm outcomes were evaluated in 37 patients with an SPN who were followed from 1970 to 2008. Thirty-three (89 %) were women, and median age at diagnosis was 32 years. Most patients were symptomatic; the most common symptom was abdominal pain (81 %). Thirty-six patients underwent resection; one patient with distant metastases was not operated on. There were no 30-day mortalities. Median tumor size was 4.5 cm. Thirty-four patients underwent an R0 resection, 1 had an R1 resection, and 1 had an R2 resection. Two patients had lymph node metastases, and one patient had perineural invasion. After resection, 34 (94 %) patients remain alive. One patient died of unknown causes 9 years after resection, and another died of unrelated causes 26 years after operation. The patient with widespread disease who didn't have resection died 11 months after diagnosis. Thirty-five of the 36 patients having resection remained disease free, including those who died of unrelated causes (median follow-up, 5 years). One patient developed a recurrence 8 years after complete resection. She was treated with gemcitabine and remained alive 14 months after recurrence. It was concluded that formal surgical resection may be performed safely and is associated with longterm survival [606].

Solid pseudopapillary tumor (SPT) of the pancreas is rare. One study was performed to analyze the expression of Wnt signal target genes (matrix metalloproteinase-7, MMP-7, cyclin-D1, and c-myc) and Ki-67 in resected SPTs to determine their clinicopathologic characteristics according to their expression. From 1995 to 2005, 23 patients underwent pancreatic resections for SPT of the pancreas. Among 23 formalin-fixed, paraffin-embedded tissues, 12 were evaluated as a pilot study. Immunohistochemistry was performed using various detection and antigen retrieval methods to detect MMP-7, cyclin-D1, c-myc, and Ki-67. The expression of Wnt target genes was correlated with clinicopathologic features of the patients. Solid pseudopapillary tumors of the pancreas always showed cytoplasmic/nuclear accumulation of beta-catenin, frequent expression of cyclin-D1, and low proliferation index. MMP-7, cyclin-D1, c-myc, and Ki-67 were not correlated with microscopic features suggesting malignant potential. Tumor size was closely related to microscopic features of malignant potential and apparently has an inverse relationship with the expression of cyclin-D1 and Ki-67. Low proliferative index and associated MMP-7 expression may cause an unpredictable clinical course in this tumor. Subtle changes in the intracellular environment, not pathologic (morphologic) changes, may elucidate the unpredictable clinical course of this tumor [607].

Solid pseudopapillary neoplasms of the pancreas (SPN) account for less than 1 percent of all pancreatic tumors. A multi-institutional retrospective review was conducted of all 21 patients who underwent surgical resection from 1994 to 2008. Twenty patients were female. Median age at presentation was 34 years. The most common presenting symptom was abdominal pain (67 %). All patients underwent resection: distal pancreatectomy (9), central pancreatectomy (6), pancreaticoduodenectomy (5), and laparoscopic excision/enucleation (1). A R(0) resection was obtained in all patients. Median tumor size was 5.5 cm. AJCC stages were stage I (18), stage II (1), stage III (2), and stage IV (0). Postsurgical complications occurred in 52 percent of patients, with pancreatic fistulae being the most common (29 %). The median follow-up time was 55 months. All patients remain alive without evidence of recurrence. It was concluded that solid pseudopapillary neoplasms of the pancreas are atypical pancreatic tumors. SPN usually occur in young women who present with abdominal pain. Oncologic outcomes in patients who undergo surgical resection are excellent [608].

Solid pseudopapillary neoplasms of the pancreas have been seen in both genders, multiple races, and at a wide range of ages. The genetic mechanism behind the development of SPN is distinct from the more lethal ductal carcinoma of the pancreas. This difference is reflected in the favorable outcome for patients with SPN. Surgery is typically curative in patients with localized disease and possibly in patients with limited metastasis or local extension. No consensus exists on an effective systemic therapy. There are no reliable predictors for disease-specific mortality or recurrence in the minority of patients who develop aggressive disease [609].

Solid psudopapillary tumor is an uncommon pancreatic neoplasm of low malignant potential that most frequently affect young woman. Solid-psudopapillary tumor are histologically, clinically, and prognostically quite distinct from the more common ductal adenocarcinoma. It was now experienced a 36-year-old male who was suspected to have extrapancreatic tumor based on atypical radiologic imaging study, young age, and male sex, and finally diagnosed as solid-psudopapillary tumor on immunohistochemical stain examination [610].

In a child

Solid pseudopapillary tumors of the pancreas are extremely rare and mostly seen in young females. It is often diagnosed incidentally or during investigations of gastrointestinal complaints. It was now reported the case of a 15-year old teenager who presented with painful abdominal tumefaction. Imaging findings were a 12 cm solid and cystic mass originating from the tail of the pancreas. A distal pancreatectomy with splenectomy was performed. Pathologic examination concluded to solid pseudopapillary tumor. Histological examination confirms the diagnosis and allows, with the help of immunohistochemical study, to rule out some differential diagnoses such as pancreatoblastoma, acinar tumors and endocrine tumors [611].

Diagnosis

The aim of one study was to investigate differential imaging features between benign and malignant solid pseudopapillary neoplasms (SPN) of the pancreas on computed tomographic and magnetic resonance imagings. Between 2001 and 2007, it was identified 30 patients with confirmed SPN by surgery. The computed tomographic and magnetic resonance images were reviewed by 3 radiologists in consensus. Each tumor was analyzed for the following categories: location of tumor, tumor margin, proportion of solid component, morphology of capsule, growth pattern, calcification, and presence of upstream pancreatic ductal dilatation. Benign SPN usually had oval/round or smoothly lobulated margins, and malignant SPN significantly more commonly had focal lobulated margins. Presence of complete encapsulation was more frequently seen in benign SPN, whereas focal discontinuity of

capsule was significantly more commonly seen in malignant SPN. There was no statistical difference between benign and malignant tumors in other imaging findings. Thus, a focal lobulated margin and a focal discontinuity of the capsule may suggest malignant SPN, whereas a round or smoothly lobulated margin and a complete encapsulation were more commonly seen in benign SPN [612].

Differential diagnosis

Pancreatic endocrine neoplasm (PEN) and solid pseudopapillary neoplasm of the pancreas (SPN) frequently pose diagnostic challenges. It was sought to determine which markers could provide the best immunophenotypic characterization of PEN and SPN, allowing separation on limited cytology samples. It was retrieved 22 resected PEN (n=12) and SPN (n=10) tumors to serve as a training set for the performance of extensive immunohistochemical staining. Based on these results, we selected a subset of antibodies for application to 25 fine-needle aspiration (FNA) samples from PEN (n=16) and SPN (n=9). Chromogranin A, synaptophysin, CD56, and progesterone receptor (PR) highlighted PEN cases in the training set; E-cadherin was noted in a membranous pattern. SPN cases were most immunoreactive for alpha$_1$-antitrypsin, vimentin, CD10, and PR, with nuclear staining for beta-catenin; E-cadherin did not show a membranous pattern. Among all FNA samples tested, the immunohistochemical staining of E-cadherin, beta-catenin, and CD10 demonstrated the greatest difference between PEN and SPN. The pattern of E-cadherin/beta-catenin expression was highly specific for distinguishing PEN from SPN. On limited FNA samples, the characteristic expression of E-cadherin/beta-catenin and the expression of CD10 can be used to distinguish PEN from SPN [613].

Solid and cystic pseudopapillary tumors

Solid and cystic pseudopapillary tumor (SCPT) is an uncommon cancer that typically affects young women. Most patients with SCPT have a favorable prognosis provided a complete resection is attained. There are anecdotal reports of the use of neoadjuvant chemotherapy or radiation therapy for patients with unresectable tumors. In one report the case of a 14-year-old female with SCPT who was successfully downsized with gemcitabine before definitive surgical resection was described [614].

Intraductal tubular carcinoma

Presented was an unusual case of intraductal tubular carcinoma, intestinal type, of the pancreas. The tumor was characterized by intraductal adenoma with a few malignant foci, and also by entire involvement of the main pancreatic duct and no involvement of its branches. A 67-year-old man was admitted to hospital because of abdominal pain. On ERCP irregular pancreatic duct was seen. No mucus secretion was observed on endoscopy. Because a biopsy showed tubular atypical cells, pancreato-duodenectomy was performed. Grossly, the entire main pancreatic duct had intraductal tumor, sparing its branches. No intraductal mucus was noted. Microscopically, the entire main pancreatic duct had proliferation of tubular adenomatous tumor without secretory mucins. Goblet cells were present in some areas. No pyloric type tubules were recognized. Malignant transformation was present in a few areas. No invasive features were recognized. On mucin histochemistry the tumor cell cytoplasm contained a little or no neutral and acidic mucus, and no secretory mucins were recognized. Immunohistochemically, the tumor cells were positive for cytokeratins (CK), CK 8, 9, 18, 19 and 20, epithelial membrane antigen, CDX2, carbohydrate antigen 19-9, and Ki-67 (labeling 30 %), MUC2, MUC5AC and MUC6, and CD10. The tumor cells were negative for C-erbB2, MUC1, trypsin, pancreatic amylase and pancreatic lipase.

The tumor cells were negative for p53 protein, but the malignant foci were positive for p53 protein and had high Ki-67 antigen (labeling 60 %). The patient was free of disease 4 years after the operation [615].

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 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 pancreaticoduodenectomy. 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 to 13 months). Adjuvant chemoradiation therapy was associated with significantly superior overall survival in patients with pancreatic adenosquamous 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 was poor. Treatment with adjuvant chemoradiation therapy was associated with improved survival. The proportion of squamous differentiation in resected pancreatic adenosquamous carcinoma specimens does not appear to impact overall survival [616].

Pancreatic lymphoma

An invasive process in the pancreas was found in a 60-year-old woman and a 50-year-old man with abdominal symptoms. Generally, such findings turn out to be adenocarcinoma. However, these patients had lymphoma. Primary pancreatic lymphoma or localization of lymphoma in the pancreas are rare and chemotherapy may be curative. Therefore, obtaining tissue for histopathological confirmation of the diagnosis is very important. Both patients underwent chemotherapy. The first patient was in complete remission one month after the last chemotherapy cycle. In the second, the disease went into remission, but he suddenly died of sepsis after the fourth chemotherapy cycle [617].

Primary pancreatic lymphoma is non-Hodgkin lymphoma primarily involving the pancreas, which is rare in pancreatic diseases. The aim of one work was to summarize the diagnostic and therapeutic experience of primary pancreatic lymphoma. It was retrospectively reviewed the clinical data of 7 cases of primary pancreatic lymphoma admitted in the past 3 years. The literature review identified 157 additional cases, and a total of 164 cases had been analyzed. In this series, only 30 percent had a successful non-operative diagnosis. The curative rate of the surgery-adjuvant chemotherapy group was higher than that of the chemotherapy alone group. Obtaining specimens through surgery is an effective diagnostic tool. Surgical resection in combination with postoperative chemotherapy plays a therapeutic role [618].

Small cell carcinoma of the pancreas

A 58-year-old man who complained of an abdominal tumor was admitted to hospital. Abdominal CT scan showed that a 15-cm tumor occupied the entire right upper abdomen and that there were ascites and liver metastases. A liver biopsy was performed. The liver biopsy showed a small cell carcinoma pattern, but no definitive origin of the tumor was determined. Considering the extensive peritoneal invasion and multiple liver metastases, the patient received 2 courses of cisplatin/etoposide chemotherapy, but his tumor became larger with concomitant abdominal pain and nausea. The patient suddenly died due to multiple organ failure caused by tumor necrosis. The autopsy revealed a pathological diagnosis of primary small cell carcinoma of the pancreas [619].

Non pancreatic periampullary tumors

Lymph node ratio (LNR) has been associated with long-term survival in patients with pancreatic adenocarcinoma; however, this has not been demonstrated in other periampullary malignancies. The purpose of one study was to determine if LNR is associated with survival in other periampullary malignancies. A retrospective review of a prospective database of 522 pancreaticoduodenectomies performed between 1988 and 2007 was undertaken. Patients with positive lymph node status were placed into the following groups: LNR = 0; LNR $\leq$ 0.2; LNR $\leq$ 0.4; and LNR >0.4. Of the 364 malignancies identified, there were 219 (60 %) pancreatic adenocarcinomas, 36 (10 %) duodenal adenocarcinomas, 75 (21 %) ampullary adenocarcinomas, and 35 (10 %) cholangiocarcinomas. Positive lymph node status affected patient survival in all malignancies studied. Increasing LNR was significabtly associated with decreased survival in both pancreatic and perimapullary cancers [620].

Papilla of Vater tumors

Carcinoids of the ampulla of Vater are the most rare primary ampullary tumors. There was noted a frequent association of the endocrine tumors with type 1 neurofibromatosis also known as von Recklinghausen disease. There are only 8 cases of papilla duodenalis minor carcinoids described in the literature. Authors describe herein the first carcinoid of papilla duodenalis minor case associated with multiple synchronic jejunal leiomyomas and von Recklinghausen disease, manifested with proximal intestinal obstruction [621].

One paper reported a case of a carcinoma that probably developed from the peribiliary gland within the ampulla of Vater based on the histopathological findings of the resected specimens. There were no malignant findings on gastrointestinal endoscopy and computed thomography. Endoscopic retrograde cholangiopancreatography revealed no tumor in the main pancreatic duct or the common bile duct or ampulla of Vater. Pylorus-preserving panctreaticoduodenectomy was performed with a diagnosis of duodenal stenosis of unknown cause. The histopathological findings revealed that a moderately to poorly differentiated adenocarcinoma originating near the peribiliary gland in the ampulla of Vater was extensively distributed in the submucosal layer of the duodenum. Based on these findings, a diagnosis of a carcinoma of the ampulla of Vater arising from the peribiliary gland was most likely [622].

A 45-year-old man: pointed out von Recklinghausen disease at 18 years of age. He had a checkup in a close inspection purpose of a duodenum tumor. It was diagnosed an accessory papilla carcinoid, and pancreas divisum was doubted. Local resection of the accessory papilla was performed and picked out a carcinoid of 7 mm size [623].

Duodenal tumors

Colorectal polyposis is the main feature of familial adenomatous polyposis (FAP), but benign and malignant lesions have also been described in the stomach, duodenum, small bowel, biliary tract and pancreas. There are few reports on FAP patients with duodenal polyps that developed at a younger age and even fewer on cases with dysplastic degeneration. The progression to carcinoma usually presents quite late in the clinical history of FAP patients, typically at least 20 to 25 years after proctocolectomy. One report described the rare case of a patient presenting with duodenal adenomas with dysplastic changes and tumor infiltration as the first sign of FAP, who was treated by pancreaticoduodenectomy followed by proctocolectomy for subsequent dysplastic changes in colonic polyps [624].

Local excision

Local surgical treatment of periampullary neoplasms seems attractive in the context of the reduced morbidity and mortality than the more radical treatment options. The aim of our study was to compare local excision of the ampulla with standard pancreaticoduodenectomy for the treatment of periampullary cancer in terms of overall survival. Inclusion criteria were primary tumor $\leq$ 2 cm with no evidence of lymph node involvement or distant metastasis on abdominal computed tomography. Between 2000 and 2004, 23 patients were enrolled onto this study (9 in the local excision group and 14 in the standard pancreatic resection group). The two groups were homogeneous with respect to age and gender as well as the size and origin of the primary neoplasm. There was no correlation of the survival with age, gender, presence of lymph node metastasis, size of the primary tumor, type of surgery or histologic grade. However, the origin of the tumor had major impact on survival, with pancreatic tumors having the worst prognosis. Hospital stay was significantly reduced in the local excision treated patients. The results showed that local excision for periampullary tumors is a viable option and is well suited for medically unfit patients or those who refuse more radical treatment options [625].

Metastases to pancreas

Metastasectomy with curative intent has become standard practice for the management of some malignancies. Resection of isolated metastatic colorectal cancer, gastrointestinal stromal tumours, neuroendocrine cancers, renal-cell cancer and sarcoma is associated with longer survival or even cure. The strongest evidence in favour of metastasectomy exists for colorectal cancer, in which resection of limited metastatic disease in some patients is associated with 5-year survival rates of more than 50 percent. High incidence of the disease, predictable tumour biology, and development of successful chemotherapies has encouraged metastasectomy. Furthermore, improved safety of complex surgeries over the past several decades has lowered the threshold for more aggressive surgical intervention. Most literature on metastasectomy pertains to the resection of disease involving the liver, lung, and brain. However, metastasectomy has been described for almost every organ system, including the pancreas. Pancreatic metastasectomy is most often done through a formal pancreatic resection such as pancreaticoduodenectomy or distal pancreatectomy. Less often, pancreatic metastasectomy is done by enucleation or a pancreas sparing operation such as a central pancreatectomy [626].

Renal cell carcinoma

Pancreatic metastasis accounts for 2 percent of metastatic renal cell carcinoma cases. Surgical management is typically recommended because of the limited value of immunotherapy as an effective treatment. Sunitinib recently showed clinical efficacy in

patients with advanced renal cell carcinoma. It was retrospectively studied a population of 15 adults with pancreatic metastasis of renal cell carcinoma at 1 center in France and at 2 in the United States who were treated with sunitinib between 2005 and 2007. Sunitinib monotherapy was given at a dose of 50 mg orally in 6-week cycles, consisting of 4 weeks of treatment followed by 2 weeks of rest. At a median follow-up of 20 months the overall tumor response using Response Evaluation Criteria in Solid Tumors was 34 percent. Median time to relapse was 20 months. Two deaths were noted but median survival was not attained. Responses in the pancreatic metastasis were seen in 28 percent of patients and were stable in 72 percent. The main grade 3 and 4 adverse events were diarrhea in 7 percent of cases and fatigue in 7 percent. Only grade 1 increased lipase was noted in 27 percent of patients and no increase in amylase was noted. Sunitinib is effective in patients with pancreatic metastasis. This raises the question of whether patients with metastatic renal cell carcinoma limited to the pancreas may derive greater clinical benefit from anti-angiogenic agents, rather than from aggressive surgical resection. However, surgery still remains the only potential cure in patients with isolated pancreatic metastasis [627].

Renal cell carcinoma (Grawitz tumor) is an epithelial tumor able, to develop, in some cases, very late metastases. The most frequent localization are: lung, bones and liver. Pancreatic metastases are rare and appear late, sometime even after 12 years from primary renal tumor. In these cases the differential diagnosis must be made with primary pancreatic tumors. It was presented a case report of pancreatic metastatic tumor developed 5 years after right nephrectomy for renal cell carcinoma [628].

Metastatic renal cell carcinoma (RCC) is a malignant tumor characterized by great variation in the clinical course and unusual sites of metastases. Metastases to the pancreas are, in general, rare. A single center experience in 10 patients with this rare presentation of metastatic RCC was presented. In most cases, the course after diagnosis of RCC pancreas metastases was relatively favorable, specifically in patients treated with surgical removal of the metastases. The median survival from the diagnosis of RCC pancreas metastases was 56 months. Long-term survival may be obtained after surgery even with suboptimal systemic therapy. An active therapeutic approach is therefore warranted in these patients [629].

Metastatic renal cell carcinoma (RCC) is a malignant tumor characterized by great variation in the clinical course and unusual sites of metastases. Metastases to the pancreas are, in general, rare. A retrospective chart review of 10 patients treated a single institution were presented. In most cases, the course after diagnosis of RCC pancreas metastases was relatively favorable, specifically in patients treated with surgical removal of the metastases. The median survival from the diagnosis of RCC pancreas metastases was 56 months. The course of disease in patients with RCC pancreas metastases is often indolent. Long-term survival may be obtained after surgery even with suboptimal systemic therapy [630].

The aim of one article was to identify patients who profit from pancreatic resection of renal cell carcinoma despite the invasiveness of the surgery. Between 1996 and 2007, data from 744 patients were collected in a prospective pancreatic surgery database, and patients with metastasis into the pancreas from renal cell carcinoma were identified. Resective surgery was performed in 14 patients with metastasis to the pancreas. Most patients were clinically asymptomatic. The median interval between primary treatment of renal cell carcinoma and occurrence of pancreatic metastasis was 94 months (range 32-158). The morbidity rate was 43 percent. Patients with a metastasis size <2.5 cm had a much better survival after resection (100 months) than those with a metastasis size >2.5 cm (44 months). Moreover, the number of metastases predicts the survival after resection. It was concluded that in patients with pancreatic metastases from renal cell carcinoma who have only limited disease, complete resection of all lesions can be successfully performed with a low rate of complications [631].

Colorectal carcinoma

Pancreatic metastases from colorectal cancer are very rare, and the possible benefit of surgical treatment is not clearly defined. One study was designed to evaluate the outcome of patients undergoing pancreatic resection for metastatic colorectal cancer to the pancreas. Nine patients underwent pancreatic resection for metastatic colorectal cancer between 1980 and 2006. The primary cancers were colon (n=7) and rectal carcinoma (n=2). The median interval between primary treatment and detection of pancreatic metastases was 33 months. In three cases pancreatic metastases were synchronous with the primary tumor. Five patients underwent pancreaticoduodenectomy, and four underwent distal pancreatectomy. A left lateral liver section and three colon resections were simultaneously performed in four patients. There was no postoperative mortality, and only two patients experienced complications. Survival averaged 20 (median, 17; range, 5-30) months: seven patients died of metastatic disease, one for unrelated disease after five months, and one is alive with liver metastases 30 months after surgery. The authors concluded that surgical resection can be performed safely in patients with isolated pancreatic metastases from colorectal cancer and in selected patients with associated extrapancreatic disease. Although long-term survival is rare, surgery should be included, whenever possible, in the multimodality approach to this disease [632].

Bronchial carcinoma

It was described the case of a 60 year old female smoker who presented with a three month history of weight loss (14 Kg), generalized abdominal discomfort and malaise. Chest radiography demonstrated a mass projected inferior to the hilum of the right lung. Computed Tomography of thorax confirmed a lobulated lesion in the right infrahilar region and subsequent staging abdominal CT demonstrated a low density lesion in the neck of the pancreas. Percutaneous ultrasound guided pancreatic biopsy was performed, histology of which demonstrated pancreatic tissue containing a highly necrotic small cell undifferentiated carcinoma consistent with metastatic small cell carcinoma of the bronchus [633].

Hepatocellular carcinoma

Fibrolamellar carcinoma is a subtype of hepatocellular carcinoma with distinct clinicopathologic features including presentation at a younger age. Although early studies suggested that fibrolamellar carcinoma had a better prognosis than conventional hepatocellular carcinoma, most later studies have found no difference. Patients often have lymph node metastases at presentation in addition to the hepatic primary. It was described an unusual case in a Thai boy who presented with a pancreatic mass that was clinically suspected to be a primary pancreatic tumor, but on biopsy was found to be metastatic fibrolamellar carcinoma. This manner of presentation has not been previously reported for fibrolamellar carcinoma, nor has metastatic spread to the pancreas [634].

Diffuse retroperitoneal cystic abdominal lymphangiomatosis

Attributed to congenital malformation of lymphatic ducts, diffuse retroperitoneal cystic abdominal lymphangiomatosis has a distribution that often corresponds to the location of primitive fetal lymphatic sacs. Three recognized types are capillary, cavernous and cystic. Multisystem involvement may occur involving spleen, liver, bone, pancreas, soft tissue, limbs and brain. Now a 55-year-old, healthy male with multiple liver lesions and retroperitoneal lymphadenopathy presented for retroperitoneal fine needle aspiration, producing 20 mL of milky liquid. Immediate cytologic evaluation showed a heterologous population of mature lymphocytes with chylomicrons. Flow cytometry revealed a polyclonal population of mature lymphocytes. Chemical analysis demonstrated a normal serum cholesterol level and an

elevated triglyceride level. Serum markers were noncontributory. It was reviewed the differential diagnostic considerations leading to obstruction or retention of lymphatic fluids (malignancy, surgical, infective and traumatic), with an emphasis on the importance of onsite cytologic evaluation, correlation with clinical history and review of the etiologic considerations. The constellation of clinical, radiologic, cytologic and laboratory findings presented in this case are diagnostic of diffuse retroperitoneal cystic abdominal lynmphangiomatosis [635].

Merkel cell carcinoma

Merkel cell carcinoma is a relatively infrequent, rapidly progressive and often fatal cutaneous malignancy exhibiting neuroendocrine differentiation. It has a penchant for local recurrence and distant metastasis to various sites, including regional lymph nodes, distant skin, lung, liver, testis and other rare organs, such as the pancreas. There are only 4 cases of Merkel cell carcinoma metastatic to the pancreas reported in the English-language literature, and they were all diagnosed by histology from pancreatic resection. A 79-year-old woman with a large pancreatic tail mass underwent endoscopic ultrasound-guided fine needle aspiration She had a history of Merkel cell carcinoma of the upper extremity with wide local excision 15 months earlier. Metastatic Merkel cell carcinoma was diagnosed based on the cytomorphology, characteristic immunohistochemical staining pattern, clinical history and comparison of the morphology with that of the primary tumor. The cytomorphology and immunohistochemical profile of this neoplasm mimicked a pancreatic endocrine tumor [636].

Pancreatic tuberculosis

Tuberculosis of the pancreas is a rare entity, and anecdotal reports describing imaging features of pancreatic tuberculosis have been described in medical literature. The imaging features including computed tomography and ultrasonography in diagnosed cases of tubercular involvement of the pancreas are described, with an overview of clinical features and laboratory investigations. It was analyzed records of 384 patients of diagnosed cases of abdominal tuberculosis for involvement of pancreas and detected 32 patients (8 %) who had pancreatic involvement. This included 22 men and 10 women with an age range of 19 to 64 years (mean age of 43 years), who were detected to have pancreatic tuberculosis from 1999 to 2004. The criteria for diagnosis of tuberculosis were based on ascitic fluid adenosine deaminase level in 14 patients, fine-needle aspiration cytology of lymph nodes in 9 patients, and presence of pulmonary tuberculosis on chest radiograph, which was found in 9 patients. On follow-up, 6 months after antituberculous treatment, 25 patients showed response to anti-Koch's treatment, 3 patients had drug-resistant tuberculosis, 2 patients died, and 2 patients were lost to follow-up. The male/female ratio was 2.2:1. The maximum number of patients was in the fourth decade (30-39 years). The duration of symptoms was spanning between 2 and 11 months, with a mean duration of 6 months. The most common symptom was abdominal pain localized to the epigastrium. Sixteen patients were seropositive for HIV-1 infection. Fourteen patients had history of tuberculosis of the lungs, whereas 18 patients had pancreatic and peripancreatic involvement as the primary manifestation. Ultrasonography showed bulky inhomogenous pancreas in 5 patients; solitary or multiple hypoechoic collections were observed in all 7 and 20 patients, respectively. CT findings demonstrated hypodense collections within the pancreas associated with peripancreatic lymphadenopathy in 29 patients. Three patients had a complex pancreatic mass lesion. It was concluded that pancreatic tuberculosis can present with a variable spectrum of imaging findings. Tuberculosis of the pancreas should be considered as a diagnostic possibility in patients who present with a pancreatic space occupying lesion associated with peripancreatic lymphadenopathy [637].

It was described a case of pancreatic tuberculosis in an immunocompromized individual. A fifty-year-old African-American gentleman with history of HIV non-compliant on anti-retroviral therapy presented with epigastric pain for five weeks duration. CT scan of abdomen showed large necrotic node on the posterior aspect of the head of pancreas and multiple cystic masses adjacent to the pancreas. Acid fast bacilli were found on staining of CT guided biopsy of the node. Cultures grew Mycobacterium tuberculosis. Anti-tubercular therapy was initiated and resulted in gradual resolution of symptoms [638].

Pancreatic involvement in tuberculosis is known but uncommon. The clinical manifestation may vary from painless obstructive jaundice due to pancreatic mass (cyst or abscess) to fever of unknown origin. It was reported a case who initially presented as acute pancreatitis relapsing into chronic pancreatitis as an initial manifestation of disseminated tuberculosis [639].

Isolated pancreatic tuberculosis (TB) is extremely rare, even in countries where TB is endemic. The recent increased reporting of TB of the pancreas is related to a worldwide increase in TB and an increase in emigration from countries where TB is endemic into countries where more sophisticated healthcare and diagnostic facilities are available. Herein, we report an unusual case of isolated pancreatic region TB, which presented with dyspeptic symptoms and was diagnosed by ultrasonography-guided needle aspiration and computed tomography scan of the abdomen. Pancreatic TB should be considered as a differential diagnosis of a pancreatic mass and most patients have an excellent clinical response to standard antituberculosis regimens [640].

PANCREATIC PSEUDOCYSTS and ANEURYSMS

Pancreatic pseudocysts

There are currently no diagnostic indicators that are consistently reliable, obtainable, and conclusive for diagnosing and risk-stratifying pancreatic cysts. Proteomic analyses were performed to explore pancreatic cyst fluids to yield effective diagnostic biomarkers in 20 prospectively recruited research participants. Sequencing of more than 350 free peptides showed that exopeptidase activities rendered peptidomics of cyst fluids unreliable; protein nicking by proteases in the cyst fluids produced hundreds of protein spots from the major proteins, making 2-dimensional gel proteomics unmanageable; GeLC/MS/MS revealed a panel of potential biomarker proteins that correlated with carcinoembryonic antigen (CEA). Conclusions: Two homologs of amylase, solubilized molecules of 4 mucins, 4 solubilized CEA-related cell adhesion molecules (CEACAMs), and 4 S100 homologs may be candidate biomarkers to facilitate future pancreatic cyst diagnosis and risk-stratification. This approach required less than 40 microL of cyst fluid per sample, offering the possibility to analyze cysts smaller than 1 cm in diameter [641].

Precepts about acute pancreatitis, necrotizing pancreatitis, and pancreatic fluid collections or pseudocyst rarely include the impact of pancreatic ductal injuries on their natural course and outcomes. It was previously examined and established a system to categorize ductal changes and it was now sought a unifying concept that may predict course and direct therapies in these complex patients. It was used a system categorizing ductal changes in pseudocyst of the pancreas and severe necrotizing pancreatitis (type I, normal duct; type II, duct stricture; type III, duct occlusion or "disconnected duct"; and type IV, chronic pancreatitis). From 1985 to 2006, a policy was implemented of routine imaging (cross-sectional, endoscopic retrograde cholangiopancreatography, or magnetic resonance cholangiopancreatography). Clinical outcomes were measured. Among 563 patients with pseudocyst, 142 resolved spontaneously (87 % of type I, 5 % of type II, and no type III, and 3 % of type IV). Percutaneous drainage was successful in 83 percent of type I, 49 percent of type II, and no type III or type IV. Among 174 patients with severe acute pancreatitis percutaneous drainage was successful in 64 percent of type I, 38 percent of type II, and no type III. Operative debridement was required in 39 percent of type I and 83 and 85 percent of types II and III, respectively. Persistent fistula after debridement occurred in 27, 54, and 85 percent of types I, II, and III ducts, respectively. Late complications correlated with duct injury. Thus, pancreatic ductal changes predict spontaneous resolution, success of nonoperative measures, and direct therapies in pseudocyst. Ductal changes also predict patients with necrotizing pancreatitis who are most likely to have immediate and delayed complications [642].

The number of patients identified with cysts of the pancreas is increasing. From 1995 to 2008, radiology records were reviewed for the presence of cystic lesions of the pancreas characteristics, patient demographics, and follow-up. Eighty-two patients met the study inclusion criteria, with a mean age at time of diagnosis of 64 years. Mean cyst size was 1.4 $\pm$ 1.1 cm, with 76 percent of patients having a solitary cyst. Thirteen patients underwent surgery. Operative intervention was statistically related to symptomatic, loculated cysts with the presence of calcifications. Malignancy was statistically related to symptomatic and loculated cysts. The data show that most pancreatic cysts found on radiographic imaging are asymptomatic, solitary, and small and can be followed safely radiographically [643].

Diagnostics

Currently, the preoperative diagnosis of a pancreatic cyst is based on clinical and imaging findings, frequently in conjunction with chemical analysis of cyst fluid and cytologic

evaluation. The purpose of these diagnostic tests is to distinguish benign from malignant cysts of the pancreas. Accordingly, it is imperative to distinguish pancreatic pseudocysts from their mimics. In one study, the authors explored the cytomorphologic features of pseudocyst of the pancreas and evaluated the role of Alcian blue and mucicarmine stains in the cytologic evaluation of pancreatic cysts. Forty-two patients were identified who had an eventual diagnosis of pancreatic pseudocyst and had an endoscopic ultrasound-guided fine-needle aspirate available. Clinical and imaging findings and chemical analyses of cyst fluid were recorded. The cytologic preparations were evaluated for gastrointestinal contamination, inflammatory cells, mucin, and pigmented material. The cytomorphologic features of 110 neoplastic mucinous cysts (intraductal papillary-mucinous neoplasms/mucinous cystic neoplasms of the pancreas) were evaluated and compared with the pseudocysts. The majority of patients (95 %) had a prior episode of pancreatitis. On imaging, the pseudocysts were unilocular (92 %). In 69 percent of cases, the endosonographic diagnosis was that of a pseudocyst. The mean carcinoembryonic antigen level was 41 ng/mL. In contrast, the cytopathologist rendered a definitive diagnosis of pseudocyst in only 10 percent of cases. The majority of smears (75 %) revealed neutrophils and/or histiocytes. Atypical epithelial clusters were identified in 3 cases, 1 of which was diagnosed as suspicious for carcinoma. Yellow pigmented material, which was identified in 13 pseudocysts (31 %), was not observed in neoplastic mucinous cysts. Alcian blue- and mucicarmine-positive material was identified in 64 and 40 percent of pseudocysts, respectively, and in 57 and 38 percent of neoplastic mucinous cysts, respectively. It was concluded that the cytologic features frequently were nonspecific. The presence of yellow pigmented material served as a surrogate marker of a pseudocyst. Special stains for mucin did not distinguish pseudocysts from neoplastic mucinous cysts [644].

To retrospectively evaluate the sensitivity and specificity of several morphologic findings that may be seen with cystic pancreatic lesions, in the diagnosis of pseudocyst at magnetic resonance (MR) imaging from 2005 to 2007, electronic radiology and pathology databases were searched to identify patients with pancreatic cystic neoplasms or pseudocysts who underwent pancreatic MR imaging. Twenty-two patients with cystic pancreatic neoplasms that were confirmed at surgical resection (n=12) or endoscopic ultrasonography with cystic fluid analysis (n=10) were identified. Of 20 patients with pancreatic pseudocysts, seven had pseudocysts that were identified at pathologic resection and 13 had a clinical history of pancreatitis, with initial computed tomography revealing no pancreatic cyst and subsequent follow-up MR imaging depicting cystic lesions. Two abdominal radiologists independently and randomly evaluated each case for presence or absence of septa and internal dependent debris and for external cyst morphology on axial and coronal T2-weighted images and three-dimensional gradient-echo T1-weighted images obtained before and after intravenous contrast agent administration. Logistic regression for correlated data was used to assess the usefulness of internal debris, external morphology, and septa for differentiating cystic neoplasms from pseudocysts. The readers' assessments of the presence or absence of cystic debris were concordant for 40 (95 %) of the 42 patients, with a kappa coefficient of 0.889, which indicated nearly perfect agreement. Thirteen (93 %) of 14 lesions found to have debris by either or both readers were pseudocysts, and only one (4 %) of the 22 cystic neoplasms had debris. Both readers were more likely to identify septa within cystic neoplasms than within pseudocysts; however, the difference was not significant for either reader. The readers were more likely to observe microlobulated morphology in cystic neoplasms than in pseudocysts, with the difference between these lesion types, in terms of prevalence of microlobulated morphology, exhibiting a trend toward-but not reaching-statistical significance. It was concluded that the presence of internal dependent debris appears to be a highly specific MR finding for the diagnosis of pancreatic pseudocyst [645].

EUS

Endoscopic ultrasound (EUS) is useful for the treatment of sterile pancreatic fluid collections (PFC), either by means of transmural drainage or by complete aspiration. The aim of one

study was to evaluate the efficacy and safety of single-step EUS-guided endoscopic approaches for treatment of sterile PFC. During a 3-year period, 77 consecutive patients with symptomatic, persistent sterile PFC were evaluated and treated with the linear EUS. It was excluded patients with grossly purulent collections, chronic pseudocyst and those whose cytology diagnostic was neoplastic cyst of pancreas. 44 patients received a single 10-Fr plastic straight stent under EUS or fluoroscopic control (group I) and 33 of these underwent a single-step complete aspiration with a 19-gauge needle (group II). The mean size of the sterile PFC was 48 mm in group I and 28 mm in group II. Overall, endoscopic treatment was successful in 70 (91 %) patients. The mean volume aspirated was 25 (18-65) ml. The total number of procedures was 50 in group I and 41 punctures in group II. After a mean follow-up of 64 $\pm$ 16 weeks there were 6 complications (14 %): 2 recurrences (referred to surgery), 2 developing abscesses (submitted a new EUS-guided endoscopic drainage with success), 1 perforation that died (2 %), and 1 case of bleeding (sent to surgery) in group I. In group II there were only 6 (18 %) recurrences (submitted a new EUS-guided aspiration). None of the patients undergoing single-step aspiration developed infections, perforation or hemorrhage. It was concluded that recurrence of pancreatic pseudocysts after endoscopic treatment was similar, either by means of plastic stents or by complete single-step aspiration [646].

Other radiology

Most pancreatic pseudocysts are common complications of acute or chronic pancreatitis. They usually occur within the pancreas or in peripancreatic tissues, and are visualized as round or oval fluid collections with thin or thick walls on computed tomography (CT) scans. However, pancreatic pseudocysts are often combined with various complications, e.g., various organ involvements, infection, hemorrhage with pseudoaneurysm formation, rupture with fistula formation, or gastrointestinal or biliary obstruction, which may necessitate prompt intervention or surgery. A review illustrates the CT appearances of various complications associated with pancreatic pseudocysts [647].

Case report

It was reporter a huge pancreatic pseudocyst migrating to the psoas muscle and inguinal region [648].

Intrahepatic pancreatic pseudocyst is an extremely rare complication of acute pancreatitis. However, it was reported a case of a 37-year old diabetic male who presented with mild pancreatitis as predicted by modified Glasgow criteria. Abdominal CT scan showed a left hepatic subcapsular cyst of 9x4 cm that progressively increased in size. CT guided aspiration of the cyst yielded 90 ml of yellow brown fluid with a high amylase concentration. Bacterial culture of the fluid was negative. The patient dramatically improved after aspiration; 3 months later the patient was asymptomatic and follow-up abdominal ultrasound has shown complete resolution of the cyst [649].

It was reported a spontaneous gastric drainage of a pancreatic pseudocyst [650].

A patient with a pancreatic pseudocyst rupture into the portal vein with a resultant noninfectious systemic inflammatory response syndrome and subsequent portal vein thrombosis diagnosed by computed tomography and ultrasonography was reported [651].

Hemosuccus pancreaticus

Erosion of peripancreatic arteries in acute or chronic pancreatitis is a rare cause of bleeding into gastrointestinal tract - hemosuccus pancreaticus. It was reported a case of a patient with chronic pancreatitis who developed acute bleeding into the gastrointestinal tract due to the

perforation of a pseudoaneurysm into pancreatic pseudocyst in the area of the pancreatic body. The diagnosis of hemosuccus pancreaticus, established by endoscopy and postcontrast CT examination, was confirmed by angiography. It was stopped the acute bleeding from pseudoaneurysm, unusually well supplied by both gastric arteries by embolization of both arteries with metallic coils. It was concluded that angiography plays an irreplaceable role in patients with hemosuccus pancreaticus. The case demonstrates bleeding from pseudoaneurysm supplied by both gastric arteries, whose embolization produced an immediate hemostasis and improvment the patient's condition [652].

Hemosuccus pancreaticus is a rare cause of upper chronic and intermittent gastrointestinal hemorrhage which cannot be easily detected by endoscopy. It is usually due to the rupture of a visceral aneurysm into the main pancreatic duct; splenic artery pseudoaneurysm associated with chronic pancreatitis represents the leading cause of this condition. The diagnosis is based on direct visualization of the hemorrhage through the main pancreatic duct at angiography. Given its rarity, difficulties in determining the source of bleeding can result in delayed treatment. It was present a rare case of true splenic artery aneurysm fistulized in the main pancreatic duct and misdiagnosed as a bleeding pancreatic pseudocyst on preoperative examination which included CT and MRCP [653].

Pancreatic aneurysm

It was presented a clinical case of successful management of an aneurysm of the inferior pancreatoduodenal artery, having resulted from occlusion of the celiac trunk and a compensatory increase in the blood flow along it from the superior mesenteric artery into the basin of the celiac trunk. In the case report described, the authors used the technique of open surgical revascularization of the celiac trunk and autovenous prosthetic repair of the aneurysmatically altered inferior pancreatoduodenal artery. The surgical decision-making was determined by the fact that the commonly accepted endovascular by-pass of the aneurysm would have resulted in the development of ischaemia in the basin of the celiac trunk and unpredictable alterations in the organs supplied thereby [654].

Although rare, a pancreatic arteriovenous malformation can have serious consequences. A diagnosis of arteriovenous malformation requires evidence of aberrant communication between the arterial and the venous systems. One report described a case where the use of multi-detector row CT and specific post-processing methods provided a diagnosis of arteriovenous malformation. This minimally invasive diagnostic approach resulted in a clear, precise and comprehensive visual representation of the pancreatic arteriovenous malformation. A 60-year-old man with right hypochondriac pain presented with a mass in the head of the pancreas. The hypochondriac pain resolved spontaneously and physical examination revealed no abnormal findings. A multi-detector row CT study was performed. The data obtained in the arterial phase demonstrated a high-contrast mass in the head of the pancreas and early enhancement of the portal vein. A maximum intensity projection method clarified the aberrant vascular communication. Changes in Hounsfield numbers were observed using a multi-planar reformation method. A volume-rendering method was used to create a 3D model which demonstrated the spatial relationship between the aberrant vascular communication and the surrounding tissue. An annual follow-up study using this technique showed no significant alteration [655].

PANCREATIC TRAUMA

Efforts to determine the suitability of low-grade pancreatic injuries for nonoperative management have been hindered by the inaccuracy of older computed tomography (CT) technology for detecting pancreatic injury (PI). A retrospective, multicenter American Association for the Surgery of Trauma-sponsored trial examined the sensitivity of newer 16- and 64-multidetector CT (MDCT) for detecting pancreatic injury, and sensitivity/specificity for the identification of pancreatic ductal injury (PDI). Patients who received a preoperative 16- or 64-MDCT followed by laparotomy with a documented pancreatic injury were enrolled. Preoperative MDCT scans were classified as indicating the presence (+) or absence (-) of pancreatic injury and pancreatic ductal injury. Operative notes were reviewed and all patients were confirmed as PI (+), and then classified as PDI (+) or (-). As all patients had pancreatic injury, an analysis of pancreatic injury specificity was not possible. PI patients formed the pool for further pancreatic ductal injury analysis. As sensitivity and specificity data were available for pancreatic ductal injury, multivariate logistic regression was performed for pancreatic ductal injury patients using the presence or absence of agreement between CT and operative note findings as an independent variable. Twenty centers enrolled 206 pancreatic injury patients, including 71 PDI (+) patients. Intravenous contrast was used in 203 studies; 69 studies used presence of oral contrast. Eight-nine percent were blunt mechanisms, and 96 percent were able to have their duct status operatively classified as PDI (+) or (-). The sensitivity of 16-MDCT for all pancreatic injury was 60 percent, whereas 64-MDCT was 47 percent. For pancreatic ductal injury, the sensitivities of 16- and 64-MDCT were 54 percent and 52 percent, respectively, with specificities of 95 percent for 16-MDCT scanners and 90 percent for 64-MDCT scanners. Logistic regression showed that no covariates were associated with an increased likelihood of detecting pancreatic ductal injury for either 16- or 64-MDCT scanners. The area under the curve was 0.66 for the 16-MDCT pancreatic ductal injury analysis and 0.77 for the 64-MDCT pancreatic ductal injury analysis. This means that both 16- and 64-MDCT have low sensitivity for detecting pancreatic injury and pancreatic ductal injury, while exhibiting a high specificity for pancreatic ductal injury. Their use as decision-making tools for the nonoperative management of pancreatic injury are, therefore, limited [656].

The authors reported a case of a grade III pancreatic injury resulting from a blunt abdominal trauma, referred to our department for observation and treated with distal splenopancreatectomy. Pancreatic traumas account for approximately 3-5 percent of blunt abdominal injuries. In cases of isolated pancreatic injuries failure to recognise injury to the Wirsung duct is the main cause of morbidity and mortality. Spiral CT with contrast medium is the standard investigation in haemodynamically stable traumatised patients, with a sensitivity of approximately 90 percent in the most recent series. However, at least initially, the extent of the pancreatic damage is not proportional to the severity of the clinical and instrumental picture. The patients need to be continuously and carefully monitored and, in the case of suspected pancreatic injury, the imaging study should be repeated 12-24 hours after the trauma. In case of doubt, ERCP provides detailed information on the condition of the Wirsung duct and, in selected cases, may play a therapeutic role through the positioning of an intraductal prosthesis. The surgical management of blunt pancreatic trauma should be individualised depending on the site and severity of the injury, the interval elapsing after the trauma and the presence of associated injuries [657].

Pancreatic trauma is rare and often missed during initial assessment of patients with abdominal trauma. One study reviewed the experience of managing pancreatic trauma at a tertiary referral center and discusses the diagnostic and therapeutic challenges. A retrospective study of a prospectively maintained hepato-pancreatico-biliary database for 12 years preceding 2007 revealed 28 patients (23 males, 10 children) with a median age of 12 years (range, 6-16 years) in children and 28 years (range, 17-54 years) in adults. Nineteen of

the 28 had pancreatic duct injury of which 15 were missed on initial evaluation and referred after conservative management (n=9) or laparotomy (n=6). Twenty-one patients developed complications including abdominal collections (n=10), pancreatic fistulae (n=9), and pseudocysts (n=2). There were 2 deaths (7 %), both of which were associated with multiple intra-abdominal injuries. At a median follow-up of 8 months (range, 3-44 months), 19 of 23 patients were asymptomatic and had been discharged from follow-up. It was concluded that pancreatic trauma in the United Kingdom is mainly the result of blunt trauma and most commonly affects young males. The presence of pancreatic duct disruption accounts for most of the complications, but in the absence of associated injuries, mortality is rare [658].

In another study the diagnosis and treatment of blunt abdominal injury to the solid organs were examined, and the differences between children and adults were highlighted. Identification of injury to the solid organs in children depends on a high index of suspicion, abnormal physical examination findings, and the judicious use of laboratory and imaging studies. Although abdominal and pelvic computed tomography with intravenous contrast remains the gold standard for imaging, it does expose children to a significant dose of radiation. Currently, more than 90 percent of solid organ injuries in children are treated nonoperatively. Abnormal hemodynamics, however, suggests active bleeding and requires operative intervention. Accurate diagnosis of the organ injured and degree of injury are important considerations for "return to play" decisions. The management of pancreatic ductal injuries is somewhat controversial, although the distal spleen preserving pancreatectomy is frequently the technique of choice. It was concluded that pediatric intra-abdominal solid organ injury is relatively uncommon, but a potential source of significant morbidity. Non-operative management is the standard of care for the majority of these injuries, although continued hemodynamic instability mandates operative intervention [659].

To evaluate the safety of nonoperative management (NOM), to examine the diagnostic sensitivity of computed tomography (CT), and to identify missed diagnoses and related outcomes in patients with blunt pancreatoduodenal injury (BPDI). Eleven New England trauma centers (7 academic and 4 nonacademic) with 230 patients (>15 years old) with BPDI admitted to the hospital during 11 years were studied. Each BPDI was graded from 1 (lowest) to 5 (highest) according to the American Association for the Surgery of Trauma grading system. Ninety-seven patients (42 %) with mostly grades 1 and 2 BPDI were selected for nonoperative management: NOM failed in 10 (10 %), 10 (10 %) developed BPDI-related complications (3 in patients in whom nonoperative management failed), and 7 (7 %) died (none related to failure of NOM). The remaining 133 patients were operated on urgently: 34 (26 %) developed BPDI-related complications and 20 (15 %) died. The initial CT missed BPDI in 30 patients (13 %); 4 of them (13 %) died but not because of the BPDI. The mortality rate in patients without a missed diagnosis was 9 percent. There was no correlation between time to diagnosis and length of hospital stay. The sensitivity of CT for BPDI was 76 percent (76 % for pancreatic and 70 % for duodenal injuries). It was concluded that the nonoperative management of low-grade BPDI is safe despite occasional failures. Missed diagnosis of BPDI continues to occur despite advances in CT but does not seem to cause adverse outcomes in most patients [660].

Trauma laparotomy is the most commonly performed procedure in the acute care setting. As current practice, removed specimens are sent for histological examination. A retrospective review of all trauma laparotomies with specimens removed and sent to pathology during a 12-month period was performed in a Level I trauma center. One hundred five procedures of 244 trauma laparotomies yielded specimens sent for examination. Eighty-six patients were male and 19 patients were female with an average age of 34 $\pm$ 14 years. Fifty-six percent of the injuries resulted from penetrating trauma and 44 percent were from blunt trauma. Gunshot wound and motor vehicle crash were the most common penetrating and blunt injuries, respectively. One hundred thirteen specimens were sent to pathology. Forty-three per cent of the specimens were spleen, 24 percent small bowel, 16 percent large bowel, 4

percent kidney, 2 percent omentum, 3 percent appendix, 3 pecent pancreas, and 1 percent for gallbladder and lung. One hundred twelve of 113 grossly normal specimens had normal pathology. One grossly normal specimen exposed abnormal pathology revealing benign appendiceal mucocele. Therefore, 99 percent of grossly normal specimens sent for histological examination after trauma laparotomy were normal. Based on this review, in select patients routine histological examination of tissues removed for traumatic injury is unnecessary [661].

ENDOCRINE PANCREATIC TUMORS

History

A search on PubMed using the keywords “neuroendocrine”, “pancreas” and “carcinoid” was performed to identify relevant literature over the last 30 years. The introduction of a revised classification of neuroendocrine tumours by the World Health Organisation (WHO) in 2000 significantly changed our understanding of and approach to the management of these tumours. Advances in laboratory and radiological techniques have also led to an increased detection of PNETs. Surgery remains the only treatment that offers a chance of cure with increasing number of non-surgical options serving as beneficial adjuncts. The better understanding of the behaviours of PNETs together with improvements in tumour localisation has resulted in a more aggressive management strategy with a concomitant improvement in symptom palliation and a prolongation of survival. Due to their complex nature and the wide range of therapeutic options, the involvement of specialists from all necessary disciplines in a multidisciplinary team setting is vital to provide optimal treatment of this disease [662].

Reported cases of diffuse nesidioblastosis have had common clinical features: postprandial hyperinsulinemic hypoglycemia, no abnormal findings in radiological examinations, and the presence of the ductulo-insular complex on histological examination. Surgical resection is recommended, but the extent of surgery is controversial. Our case had some clinical features of insulinoma but was diagnosed as diffuse nesidioblastosis according to histopathologic criteria. Because arterial stimulation and veneous sampling showed that the pancreatic body and tail had a lesion producing insulin abnormally, we performed a distal pancreatectomy to cure the hypoglycemia. Clinically, it is very difficult to distinguish diffuse nesidioblastosis from insulinkoma [663].

Genetics

Pancreatic endocrine neoplasms (PENs) are diagnostically challenging tumors whose natural history is largely unknown. Histopathology allows the distinction of two categories: poorly differentiated high-grade carcinomas and well-differentiated neoplasms. The latter include more than 90percent of PENs whose clinical behavior varies from indolent to malignant and cannot be predicted by their morphology. The diagnosis of PEN is generally easy, but unusual features may induce misdiagnosis. Immunohistochemistry solves the issue, provided that the possibility of a PEN has been considered. Morphology allows the distinction of poorly differentiated aggressive carcinomas from well-differentiated neoplasms. The World Health Organization classification criteria allow for the discernment of the latter into neoplasms and carcinomas with either benign or uncertain behavior. The recently proposed staging and grading systems hold great promise for permitting a stratification of carcinomas into clinically significant risk categories. To date, inactivation of the MEN1 gene remains the only ascertained genetic event involved in PEN genesis. It is inactivated in roughly one-third of PENs. The degree of genomic instability correlates with the aggressiveness of the neoplasm. Gene silencing by promoter methylation has been advocated, but a formal demonstration of the involvement of specific genes is still lacking. Expression profiling studies are furnishing valuable lists of mRNAs and noncoding RNAs that may advance further the research to discover novel markers and/or therapeutic targets [664].

Gastrointestinal and pancreatic neuroendocrine tumors (GEP-NETs) originate from cells of the diffuse endocrine system. Most GEP-NETs are sporadic, however, some of them, especially pancreatic endocrine tumors, may occur as part of familial syndromes. The genetic and molecular pathology of neuroendocrine tumor development is incomplete and remains largely unknown. However, the WHO classification introduced in clinical practice will

give more insight into genetic and molecular changes related to tumor subtypes. In sporadic endocrine pancreatic tumors, losses of chromosome 1 and 11q as well as gain on 9q appear to be early invents in development of pancreatic tumors because they are already present in small tumors. Multiple genetic defects may accumulate with time and result in pancreatic neuroendocrine tumor progression and malignancy. Gastrointestinal endocrine tumors (carcinoids) show predominantly genetic alterations concentrated on chromosome 18. There are losses of the entire chromosome as well as smaller deletions. The most frequently reported mutated gene in gastrointestinal neuroendocrine tumors is b-catenin. Overexpression of cyclin D1 and cMyc has also been reported. Recently, a set of genes NAP1L1, MAGE-2D and MTA1 has been correlated with malignant behavior of small intestinal carcinoids. It was concluded that molecular profiling of GEP-NETs demonstrates that pancreatic endocrine tumors and gastrointestinal neuroendocrine tumors (carcinoids) display different genetic changes and should, therefore, be considered to be different tumor entities; thereby, also differently managed clinically. Although the number of genetic changes is higher in malignant tumors, we are still far away from defining a malignant profile in GEP-NETs [665].

Familial endocrinopathias

The development of genetic testing has given patients with familial endocrine diseases the opportunity to be identified earlier in life. The importance of this technological advancement cannot be underestimated, as some of these heritable diseases have significant potential for malignancy. One article focused on the identification and surgical management of familial endocrinopathies of the thyroid, parathyroid, adrenal glands, and pancreas. Familial endocrinopathies discussed include hereditary nonmedullary carcinoma of the thyroid, Cowden disease, familial adenomatous polyposis, Carney complex, Werner syndrome, familial medullary thyroid carcinoma, Pendred syndrome, hereditary hyperparathyroidism jaw-tumor syndrome, familial isolated hyperparathyroidism, Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, neurofibromatosis I, von Hippel-Lindau disease, and tuberous sclerosis [666].

Multiple endocrine neoplasia

Multiple endocrine neoplasia syndrome type 1 (MEN-1) consists of endocrine tumors of the parathyroid, the endocrine pancreas-duodenum, and the pituitary. Surveillance and screening for the endocrinopathies is recommended in gene carriers. Surgery for MEN-1-related hyperparathyroidism is generally performed as radical subtotal parathyroidectomy, because less surgery is likely to result in persistent or recurrent disease. Multiple endocrine neoplasia syndrome type 2 (MEN-2) consists of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Prophylactic thyroidectomy based on DNA testing in the MEN-2 syndrome is considered one of the greater achievements in cancer treatment, because it may be performed before thyroid carcinoma development and provides cure for the patient [667].

The purpose of one study was to describe outcomes of MEN-1 patients with recurrence requiring completion pancreatectomy and duodenectomy after initial treatment of pancreatic endocrine neoplasms (PENs) and hypergastrinemia with distal pancreatectomy, enucleation of pancreatic head PENs, and duodenotomy. After undergoing this initial operation, 8 of 49 patients (16 %) required completion pancreatectomy and duodenectomy for recurrent PENs and hypergastrinemia. Median age was 39 years (27-51) at completion pancreatectomy compared to 31 years (20-40) at initial operation. Pathology revealed multiple PENs in 100 percent, duodenal neoplasms in 63 percent, and metastatic lymph nodes in 75 percent. There was no operative mortality and 88 percent of patients are currently alive. Preoperative gastrin levels were 934 $\pm$ 847 pg/mL while postoperative levels were 93 $\pm$ 79 pg/mL (normal

25-111 pg/mL). Mean Hemoglobin A1C levels are 8.3 ± 3.3 percent (normal 3.8-6.4 %). This initial operation may provide tumor control and prevent metastases but recurrent PENs are multifocal and progressive. Completion pancreatectomy and duodenectomy is arduous but outcomes are acceptable. Considering the radical nature of this treatment, individual consideration should be given to MEN-1 patients amenable to initial alternative pancreatic resections that preserve pancreatic mass and allow future pancreas-preserving reoperations [668].

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal syndrome caused by mutations in the MEN1 tumor suppressor gene. Whereas the protein product of MEN1, menin, is ubiquitously expressed, somatic loss of the remaining wild-type MEN1 allele results in tumors primarily in parathyroid, pituitary, and endocrine pancreas. To understand the endocrine specificity of the MEN1 syndrome, it was evaluated biallelic loss of Men1 by inactivating Men1 in pancreatic progenitor cells using the Cre-lox system. Men1 deletion in progenitor cells that differentiate into exocrine and endocrine pancreas did not affect normal pancreas morphogenesis and development. However, mice having homozygous inactivation of the Men1 in pancreas developed endocrine tumors with no exocrine tumor manifestation, recapitulating phenotypes seen in the MEN1 patients. In the absence of menin, the endocrine pancreas showed increase in cell proliferation, vascularity, and abnormal vascular structures; such changes were lacking in exocrine pancreas. Further analysis revealed that these endocrine manifestations were associated with up-regulation in vascular endothelial growth factor expression in both human and mouse MEN1 pancreatic endocrine tumors. Together, these data suggest the presence of cell-specific factors for menin and a permissive endocrine environment for MEN1 tumorigenesis in endocrine pancreas. Based on this analysis, it was proposed that menin's ability to maintain cellular and microenvironment integrity might explain the endocrine-restrictive nature of the MEN1 syndrome [669].

To investigate if transcription factors involved in pancreatic differentiation and regeneration are present in pancreatic endocrine tumors and if they are differentially expressed in normal pancreas compared with multiple endocrine neoplasia type 1 (MEN1) nontumorous pancreas the expression of neurogenin 3 (NEUROG3), neurogenic differentiation 1 (NEUROD1), POU class 3 homeobox 4 (POU3F4), pancreatic duodenal homeobox factor 1 (PDX1), ribosomal protein L10 (RPL10), delta-like 1 homolog (DLK1), and menin was analyzed by immunohistochemistry in normal pancreas and pancreatic endocrine tumors from 6 patients with MEN1 and 16 patients with sporadic tumors, as well as pancreatic specimens from Men1 heterozygous and wild type mice. Quantitative polymerase chain reaction was performed in a subset of human tumors. Tumors and MEN1 nontumorous endocrine cells showed a prominent cytoplasmatic NEUROG3 and NEUROD1 expression. These factors were significantly more expressed in the cytoplasm of Men1 heterozygous mouse islet cells compared with wild type islets; the latter showed an exclusively nuclear reactivity. The degree of Pou3f4, Rpl10, and Dlk1 immunoreactivities differed significantly between islets of heterozygous and wild type mice. The expressions of RPL10 and NEUROD1 were prominent in the MEN1 human and heterozygous mouse exocrine pancreas. Insulinomas had significantly higher PDX1 and DLK1 messenger RNA levels compared with other tumor types [670].

Diagnostics

The aim of one study was to characterize the ultrasonographic features of neuroendocrine tumors (NET) and their metastases with contrast-enhanced ultrasonography (CEUS) and to compare this to clinical data. During a period of 5 years, 82 patients with 83 histologically proven NET were prospectively examined using conventional US and pulse inversion US with a second generation contrast agent (SonoVue, Contrast Pulse Sequencing) focusing on

the arterial (10-20 sec p. i.), capillary (20-25 sec p.i.), portal venous (25-120 sec p.i.), and late phases (>120 sec p.i.). 69 patients had metastases in the abdominal tract, including eight patients with poorly differentiated neuroendocrine carcinomas with high-grade behavior. In 31 patients the proliferation index (MIB-1) of the NET was ≤ 2 percent, in 46 patients > 2 percent, and in 6 patients ≥ 20 percent. Thirteen patients had one primary lesion without metastases. In NET of the lung, stomach, and colon it was found only hypoechoic or isoechoic liver metastases. NET of the small intestine and pancreas represented hypoechoic, isoechoic, and/or hyperechoic liver lesions, sometimes combined. Insulin producing tumors (6) had hypoechoic metastases. Necrotic areas (25/83) were detected after interferon therapy, embolization, systemic chemotherapy, and radiofrequency ablation of liver metastases, but did not develop after somatostatin receptor radionuclide therapy. In large NET (> 3 cm) with a proliferation index of > 2 percent, necrotic areas appeared spontaneously. In 93 percent (77/83) of the cases the NET and their metastases showed an early arterial influx of microbubbles. Rim-like contrast enhancement occurred during the capillary phase in 78 percent (65/83) of all lesions, and hypervascularization occurred during the arterial phase and at the beginning of the capillary phase in 95 percent (79/83). The hypervascularized tissue was found in the primary lesions, in liver, lymph node metastases and any kind of abdominal metastases. In liver metastases with a proliferation index >2 percent, tumor arteries showed a chaotic growth pattern. In 93 percent (77/83) the NET lesions appeared as dark "defects" at the beginning of the late phase. It was concluded that CEUS with CPS demonstrates typical NET imaging characteristics. In most cases real-time CEUS may replace other imaging techniques [671].

Gastro-entero-pancreatic neuroendocrine tumours (GEP NET) represent a rare and highly heterogeneous entity that often is revealed by vague and non-specific symptoms, leading to a delayed diagnosis. Here we will review some of the most regularly observed false positive and false negative cases and provide clues to recognize and manage them properly. Particularly, the value of chromogranin-A as a serum tumour marker and Somatostatin receptor scintigraphy as an imaging test, were reviewed. Indeed, chromogranin-A and other hormones, such as gastrin, as well as urinary 5-hydroxy-indolic acetic acid (5-HIAA) are often tested to diagnose NET without appraising the clinical situation, leading to extensive work-up on false bases. On the other hand, some tests are performed in situations where they do not add additional information (e.g. 5-HIAA in pancreatic or rectal NET) because invariably negative. Somatostatin receptor scintigraphy is an expensive examination for which indications must be carefully assessed, knowing its specificity and sensitivity [672].

Somatostatin analogs
Somatostatin analogs (SSAs) have an important role in the management of patients with neuroendocrine tumours of the gastrointestinal tract and pancreas (GEP NETs). These compounds can control the symptoms induced by the production of hormones and peptides. The antiproliferative effects of SSAs and especially tumour shrinkage are less obvious in patients with GEP NETs than in those with acromegaly. However, based upon phase II experience there is a strong suggestion of a disease stabilizing effect of SSAs in selected patients. Those patients with a progressive, non-functional GEP NET, positive octreotide scintigraphy, a low proliferation index and in the absence of surgical options may benefit from a first-line medical therapy with SSAs. The exploration of the mechanisms of this effect is unclear and hampered by the lack of suitable preclinical models. The better understanding of the tumour biology of GEP NETs, together with the development of new SSAs with better affinity on all somatostatin receptors, represent an unmet medical need [673].

Somatostatinoma

Somatostatinoma is a rare somatostatin-producing endocrine tumor, probably malignant. Due to its nonspecific symptoms such as vague abdominal pain, weight loss, or occult

clinical features, misdiagnosis occurs. It was reported a case of pancreatic somatostatinoma with severe hypoglycemia. The patient had experienced severe hypoglycemic attacks for 11 months periodically. Contrast computed tomography scan revealed an isodensity mass about 2 cm in the head of the pancreas. Ultimately, a local excision was carried out as the tumor was located exactly on the surface of the pancreas. Somatostatinoma was established after immunohistochemical technique. The patient led a normal life without any complaint at 1 year follow-up [674].

VIPoma

Clinical manifestations, laboratory examination, imaging features, surgical findings, and pathological findings of four patients with VIPoma admitted from 1991 to the present were discussed. Watery diarrhea and hypokalemia were the main clinical manifestations. Hepatic metastasis occurred in 2 patients. The pancreatic body and tail were the main locations of lesions. Two tumors were shown in the pancreatic body and tail in 1 patient. Two patients with hepatic metastases received a combination therapy of octreotide, surgery, and chemotherapy, which resulted in symptom improvement and normalization of the serum potassium values. Distal pancreatic resection and second resection of hepatic metastatic lesions were performed in 1 patient. Resection of the pancreatic body and tail was done in 1 patient, and pancreatoduodenectomy was performed in another patient. Laparotomy was done in 1 patient because of invasion of the superior mesenteric vein and duodenum [675].

Zollinger-Ellison syndrome

Most patients with Zollinger-Ellison Syndrome (ZES), even those in whom gastrinoma is found and resected at initial operation, will suffer from persistent or recurrent disease in longterm followup. There is currently no consensus about managing patients with recurrent or persistent ZES. It was performed a review of a consecutive series of patients evaluated and managed at our institution between 1970 and 2007 for ZES. "Biochemical cure" was defined as normal serum gastrin assays and negative imaging studies. Reoperations were performed for elevations in serum gastrin assays and positive findings on imaging studies. Fifty-two patients with sporadic ZES were analyzed. Median followup was 14 years. Among patients with sporadic ZES, 37 patients underwent operative management. The most common operations were resection of duodenal gastrinoma (n=8) and total gastrectomy (n=7). Nine patients underwent 15 reoperations for recurrent or persistent disease. "Biochemical cure" was obtained in four patients (44 %) undergoing reoperation for ZES. Three of these patients remained without evidence of recurrence at 4, 9, and 12 years after their curative re-resection. Only one of nine patients who underwent reoperation died of metastatic gastrinoma. It was concluded that primary and reoperative surgery in patients with sporadic ZES results in a significant rate of "biochemical cure." In selected patients with recurrent or persistent disease, reoperation for resection of gastrinoma is associated with excellent longterm survival and is warranted [676].

Insulinomas

Insulinoma is a rare neuroendocrine tumor with an incidence of 4 per 1 million persons per year, which may occur as a unifocal sporadic event in patients without an inherited syndrome or as a part of multiple endocrine neoplasia type 1. Key neuroglycopenic and hypoglycemic symptoms in conjunction with biochemical proof establish the diagnosis. Once the diagnosis is established, the insulinoma is preoperatively localized within the pancreas with the goal of surgical excision for cure [677].

Insulinomas are rare neuroendocrine tumours with an incidence of four cases per million a year. Only few cases of insulinoma in patients with preexisting diabetes mellitus have been reported. It was presented a 50-year-old male with type 2 diabetes mellitus who suffered from recurring hypoglycemia. He had gained 20 kilograms of weight in five years. 72-hour fast revealed hypoglycaemia in the presence of inadequately high C-peptide and insulin levels. Magnetic resonance imaging and selective arterial calcium stimulation test confirmed a mass in the body of the pancreas. The tumor was removed surgically. Pathological examination demonstrated a benign insulinoma. Postoperatively, blood glucose levels were within the therapeutic range. The HbA (1c) value was 6.8 percent three months after the intervention. Clinicians should be alert to insulinoma as a, though rare, differential diagnosis of hypoglycaemia in diabetes, in particular in patients with recurrent, otherwise unexplained hypoglycaemia [678].

Non-functioning tumor

A 52-year-old man was admitted for detailed examination of a mass with extensive calcification in the tail of the pancreas by fluoro-deoxy glucose-positron emission tomography/computed tomography (FDG-PET/CT). Abdominal CT and magnetic resonance imaging (MRI) findings showed a calcified tumor 5 cm in diameter with a smooth surface. The tumor mainly showed calcification at it center and a partially solid element around it margin which was enhanced in the early phase. Pathological and immunohistochemical studies revealed a nonfunctioning islet cell tumor with calcification. A nonfunctioning islet cell tumor with central calcification formation as it grew to a maximum diameter of 7 cm is rare. When diagnosing pancreatic tumors it must be kept in mind that some nonfunctioning islet cell tumors of the pancreas can show nontypical features such as calcification formation [679].

Tumors of the papilla of Vater

Endocrine tumors of the ampullary region are rare, and accurate indications for their management are lacking. It was reviewed all patients who 1982-2003 were submitted to a pancreaticoduodenectomy for ampullary endocrine tumors. Eight patients, 3 men and 5 women, with a mean age of 48 years were included. Two patients presented with Zollinger-Ellison syndrome, and 1 had neurofibromatosis. Operative mortality was nil. The mean size of the tumors was 17 mm (range, 5-40 mm). There were 7 well-differentiated and 1 poorly differentiated endocrine carcinomas. Seven patients had satellite lymph node metastases, and 1 had diffuse liver metastases. Median follow-up was 131 months (range, 17-315 months). At the end of the follow-up period, 5 patients were alive and disease-free; 1 patient was alive with stable liver metastases. Two patients died 17 months and 13 years after surgery, respectively, from metastasis and an unrelated cause. This study demonstrates the high frequency of lymph node invasion in these uncommon tumors, even at an early clinical stage. Pancreaticoduodenectomy may result in prolonged survival of patients with well-differentiated tumors [680].

Surgery

Surgery represents the only chance of cure for a patient with a neuroendocrine tumour (NET). The main indications for surgery lie in the risk of developing metastatic disease with increasing tumour diameter and for a functioning NET also in control of the hormonal syndrome. However, only a small minority of patients presents with a potentially resectable primary NET without metastatic disease. An R0-resection is mandatory, which may be

achieved in selected cases by tissue sparing surgical techniques. Most patients unfortunately present with a locally advanced or metastatic disease. For patients with an advanced functioning NET, control of the hormonal syndrome may also represent a surgical indication. Various cytoreductive techniques or, in highly selected cases, liver transplantation can be applied. For locally advanced non-functioning tumours, there is an indication for surgery in large tumours which tend to create local complications because of bleeding or bowel obstruction. Especially in ileal NETs aggressive surgical therapy is recommended because of prevention of long-term complications, which may improve survival [681].

Medical treatment

The incidence of pancreatic endocrine tumor (PET) accounts for approximately 2 percent of total pancreatic tumors and for approximately 1.5 pecent of autopsy cases, reflecting the recently increasing trend. According to WHO criteria (2004), PET is classified by the type of hormone produced by the tumor and its biological behavior. Together with the classical clinical images and hormone markers, ^{11}C-5-HTP-Positron emission tomography, OctreoScan (^{111}In-DTPA0-octreotide)scintigram, SACI-test and IOUS are used for diagnosis. Surgery is the treatment of choice, if supposed to be curative and tolerable. In case of a well-differentiated endocrine tumor, with no indication of resection or IVR, somatostatin analog is another therapy showing stable disease status for a long period. Systemic chemotherapy, including 5-FU+streptozotocin, and streptozotocin+doxorubicin, are used in cases of well -differentiated endocrine carcinoma, and cisplatin+etoposide are applied for poorly-differentiated endocrine carcinoma (or small cell carcinoma). Recent studies focus on molecular target therapy including small molecules and monoclonal antibody, such as tyrosine kinase inhibitor, anti-VEGF antibody and moor inhibitor [682].

Cytotoxic treatment

Gastroenteropancreatic neuroendocrine tumours (GEP NET) are heterogeneous and rare malignancies although their prevalence is increasing. Multiple therapeutic approaches are available to date for their management, including surgery, hormonal and immune radionucleide therapies and chemotherapy. The purpose of one review was to collect, examine, and analyze data available regarding contemporary chemotherapeutic management of GEP NET in order to determine whether or not chemotherapy still takes place in the therapeutic arsenal of GEP NET. Anthracyclins, 5-fluorouracil (5-FU), DTIC and streptozotocin are amongst the most commonly used chemotherapeutic agents, usually prescribed in combination. Their efficiency in reducing tumor burden is not always associated with better survival, perhaps due to severe toxicity. Chemotherapy in GEP NET is mainly devoted to poorly differentiated tumours, but also in well differentiated carcinomas either not eligible or resistant to other therapies. Chemotherapy remains therefore useful in specific cases of GEP NET management. However, a new era of antitumoral agents, such as targeted therapies, could eventually replace these old recipes in the near future [683].

Radiolabeled targeted therapies

Gastro-entero-pancreatic neuroendocrine tumours (GEP NET) are a heterogeneous group of proliferative disorders whose management dramatically relies on tumour biology. For well-differentiated, low-proliferative index tumours, locoregional treatment and targeted radioisotopic therapies offer an attractive and seemingly efficient alternative to palliative surgical resections. Lack of well-designed, prospective, randomized multicentric studies hinders a balanced evaluation of available locoregional treatment methods: embolization, chemo-embolization, radio-embolization. According to available datas, all techniques achieve a 50-60 percent radiological response rate and almost 80 percent of symptomatic relieve for the patients, while their impact on progression-free and overall survival remains not

assessable. Same conclusions can be drawn for radiolabeled targeted therapies like MetaiodoBenzylGuanidine (MIBG) and Peptide Receptor Radionuclide Therapy (PRRT), which, provided that their target is expressed by tumour cells, can deliver therapeutic doses of radiation to neoplastic tissues. ^{131}I-MIBG has been associated with a 50 percent symptomatic response rate and mainly haematological toxicities. PRRT with ^{111}In-DiethyleneTriamineentaacetic Acid-Octreotide, [90Y-DOTA0-Tyr3]-Octreotide, or [177Lu-DOTA0-Tyr3]-Octreotate seem to alleviate symptoms in 50 percent of patients and obtain a radiological response in 30-38 percent. Renal toxicity, partially preventable, is more frequent than previously thought and result in an annual decrease in glomerular function by 4 to 8 percent per year. Forthcoming research in GEP NET should by a majority be designed in randomized, prospective and multicentric fashion. Locoregional disease trials must focus on clinical outcome differences between embolization techniques (embolization, chemoembolization and radioembolization) and surgery. In disseminated disease, studies should assess radiolabeled targeted therapies efficiency when administered along with and compared to new biological and older chemotherapeutic agents [684].

Metastatic endocrine cancers

Pancreatic endocrine carcinomas (PECAs) are uncommon, with an incidence of 1 per 100,000. Past studies of chemotherapy and hepatic arterial embolization have described median survival durations of approximately 2 to 3 years. Overall survival from time of diagnosis of metastases has never been reported in a large cohort of patients. The objective of one study was to evaluate the stage-specific prognosis of patients with metastatic PECAs and to assess the impact of clinical and pathologic prognostic factors. It was evaluated all cases of differentiated, metastatic PECAs seen at a cancer center between the years 1999 and 2003, measuring survival from time of diagnosis of metastases. Ninety cases of metastatic PECAs were identified. Median overall survival was 70 months, and the 5-year survival rate was 56 percent. Age, sex, and tumor type (functional vs nonfunctional) did not impact prognosis. Tumor grade, however, was highly prognostic for survival. The prolonged survival duration may reflect the impact of multimodality treatments. Tumor grade (low vs intermediate grade) represents a highly significant prognostic factor [685].

Panniculitis

The association between pancreatic panniculitis and pancreatic disease is well described, but differentiation among the neoplastic causes of the syndrome remains difficult due to substantial overlap in histological and immunohistochemical features. It was reported a case of subcutaneous fat necrosis as the presenting feature in a 61-year-old man with metastatic carcinoma of pancreatic origin. Previous pathological evaluation of the patient's liver biopsy led to an initial diagnosis of adenocarcinoma of unknown primary site. One month later, the patient presented with pancreatic panniculitis, prompting further investigation. Immuno-histochemistry was consistent with neuroendocrine differentiation, but the patient rapidly decompensated and died before the evaluation was complete, leaving the definitive diagnosis in question. In a review of the published reports of tumor types associated with pancreatic panniculitis, it was found that immunohistochemical staining and electron microscopy can and should be used in conjunction with clinical correlation to accurately differentiate neuroendocrine tumors from carcinomas with acinar cell features [686].

Overall survival

Pancreatic neuroendocrine tumors (pNETs) are an uncommon pancreatic neoplasm. It was reviewed the presentation, management, and outcome of patients with pNETs treated at a single center by a multidisciplinary approach between 2004 and 2008. Over this time period, 154 patients with carcinoid and neuroendocrine tumors were treated, which included 46 patients (30 % of total) with pNETs. The most common presentations included abdominal pain (43 %), systemic symptoms such as hypoglycemia (33 %), and incidental mass (15 %). Fourteen patients had functional tumors. At the time of diagnosis, 22 patients (48 %) presented without metastases and 24 (52 %) had metastatic disease. Median follow up for the entire group was 42 months. All patients with nonmetastatic pNET underwent pancreatic resection with 95 percent postoperative survival. Overall survival in this group at 3 years was 86 percent and disease-free survival was 81 percent. In patients presenting with metastatic pNET, multiple treatment modalities were used, including liver resection or ablation (n=15), hepatic chemoembolization (n=17), pancreatic resection (n=12), and systemic treatments (n=7). Three-year survival was 70 percent. Pancreatic resection results in greater than 80 per cent 3-year survival in nonmetastatic pNET. In patients presenting with metastatic pNET, excellent survival rates are also achievable using a multidisciplinary multimodal approach [687].

Pancreatic endocrine tumors (PETs) are infrequent, which makes large experiences unlikely. The aim was to describe a large single-center experience with PETs and the use of endoscopic ultrasound (EUS) and a cancer staging system (TNM). This study involves a retrospective analysis of 86 patients (44 men) who underwent EUS-fine needle aspiration (EUS-FNA). Immunohistochemistry was used. Typical EUS features were well-demarcated, hypoechoic, solid, homogeneous lesions. Ninety percent had the diagnosis obtained by EUS-FNA. Twelve PETs (14 %) were functioning, 8 (9 %) were cystic, and 14 (16 %) were 10 mm or smaller. Nonfunctional PETs and larger lesions were more advanced. The TNM stage was I in 24, II in 10, III in 18, and IV in 34 patients. Sixteen patients (27 %) died, and 30 patients (52 %) had progression or recurrence during the follow-up (34 $\pm$ 27 months). TNM stage and surgery with curative intent were related to progression. The overall 5-year survival was 60 percent. The mean survival time was 94 $\pm$ 12 months for stage I, 52 $\pm$ 12 months for stage III, and 54 $\pm$ 7 months for stage IV. It was concluded that nonfunctional PETs were more common and advanced. The EUS-FNA has a high accuracy for diagnosing PETs. Progression and poorer survival were associated with TNM stage [688].

To identify potential preoperative prognostic factors in resected pancreatic and periampullary neuroendocrine tumours clinico-pathological data for 54 consecutive patients with pancreatic or periampullary neuroendocrine tumors referred over a 10-year period were identified from a prospective database. Thirty-four patients underwent pancreatic resection (12 males, median age 54 years). There was a single 30-day mortality (3 %). Nodal status, microscopic resection margin involvement, and tumor size failed to exhibit any prognostic value. Only the presence of malignant tumor characteristics was significantly associated with poorer overall survival. Analysis of preoperative parameters showed that age >60 years, platelet-lymphocyte ratio >300, alkaline phosphatase levels >125 U/l, and alanine aminotransferase >35 U/l were adverse prognostic factors. A risk stratification score was generated where each adverse preoperative parameter was allocated a score of 1. A cumulative score of < 1 was defined as low risk, while a score of > 2 was defined as high risk. Median overall survival in the high-risk group was 10 months, while the median survival in the low-risk group was >60 months. It was concluded that significant prognostic information can be gained from routine preoperative biochemistry and haematology results in resected pancreatic and periampullary neuroendocrine tumours [689].

Quality of life

To develop a disease-specific questionnaire for identifying domains having the greatest impact on the quality of life (QOL) of patients with neuroendocrine tumors (NETS) patient responses to clinical interviews provided an 80-item initial pool for the development of the QOL-NET. The Delphi panel reviewed the items for content validity; the patient focus group reviewed the items for content/readability. Domains were derived from analysis of224 questionnaire responses. After principal components analysis, a scree plot suggested 7 domains. Exploratory factor analysis with forced 7-factor varimax rotation determined an ideal structure. Reliability/reproducibility was determined by test/retest 4 to 6 weeks apart. Logistic regression determined each domain score. All 7 domains exhibited strong internal consistency. Physical functioning contributed 40 percent of the total QOL score, followed by flushing, gastrointestinal symptoms, respiratory, cardiovascular, depression, and attitude domains. Most items loaded 0.40 or higher. No significant differences in test and retest scores. The mean values for the total QOL and 4 of 7 factor scores were significantly higher for NETS than controls: sensitivity was 71 percent and specificity was 70 percent to discriminate the NETS from the controls. Thus, though the QOL-NET is reliable and reproducible it only weakly identifies NETS [690].

REFERENCES

001. Metter CC. History of Medicine. Philadelphia, PA: The Blakiston Co, 1947.

002. McClusky DA, Skandalakis LJ, Colborn GL, Skandalakis JE. Harbinger or hermit? Pancreatic anatomy and surgery through the ages – part 1. World J Surg 2002; 26: 1175-85.

003. Modlin IM, Kidd M. The paradox of the pancreas: from Wirsung to Whipple. Hanover, Germany: Politzki Print Productions, 2003.

004. Daremberg C, Ruelle E. Oeuvres de Rufus d'Ephese. Paris: L'Imprimerie Nationale, 1879.

005. Howard JM, Hess W. History of the pancreas: mysteries of a hidden organ. New York: Kluwer Academic/Plenum Publishers, 2002.

006. Vesalius A. De Corporis humani fabrica. Basel, Switzerland: Joannes Oporinus, 1543.

007. Howard JM, Hess W, Traverso W. Johann Georg Wirsung (1589-1643) and the pancreatic duct: the prosector of Padua, Italy. J Am Coll Surg 1998; 187: 201-11.

008. Stern CD. A historical perspective on the discovery of the accessory duct of the pancreas, the ampulla “of Vater” and pancreas divisum. Gut 1986; 27: 203-12.

009. Oddi R. D'une dispositiona sphincter speciale de l'ouverture du canal choledoque. Arch Ital Biol 1887; 8: 317-22.

010. Pannala R, Kidd MP, Modlin IM. Acute pancreatitis: a historical perspective. Pancreas 2009; 38: 355-66.

011. Kidd M, Modlin IM. The luminati of Leiden: from Bontius to Boerhaave. World J Surg 1999; 23: 1307-14.

012. Foster M. Lectures on the history of physiology during the sixteenth, seventeenth, and eighteenth centuries. London: Cambridge University Press, 1924.

013. Brunner JC. Experimenta nova circa pancreas. Amsterdam: Wetstenius, 1683.

014. Busnardo AC, DiDio LJ, Tidrick RT, Thomford NR. History of the pancreas. Am J Surg 1983; 146: 539-50.

015. Bernard C. Du suc pancreatique et de son role dans les phenomenes de la digestion. Mem Soc Biol 1849; 1: 99-115.

016. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. J Physiol 1902; 28: 325-53.

017. Mutt V. Historical perspectives in cholecystokinin research. Ann N Y Acad Sci 1994; 713: 1-10.

018. Galen C. On the usefulness of the parts of the body. May MT, translator. New York: Cornell University Press, 1968.

019. Bigsby JJ. Observations, pathological and therapeutic, on diseases of the pancreas. Edinb Med Surg J 1835; 44: 85-102.

020. Claessen H. Die Krankheiten des Pancreas. Cologne, Germany: DuMont-Schaumberg, 1842.

021. Ragland ER. Experimenting with chymical bodies: Reinier de Graaf's investigations of the pancreas. Early Sci Med 2008; 13: 615-64.

022. Tonsi AF, Bacchion M, Crippa S, Malleo G, Bassi C. Acute pancreatitis at the beginning of the 21st century: the state of the art. World J Gastroenterol 2009; 15: 29-45.

023. Pannala R, Kidd M, Modlin IM. Acute pancreatitis: a historical perspective. Pancreas 2009; 38: 355-66.

024. Tulp N. Observationum medicarum. Editio nova et actua [Medical Observations. New and Enlarged Edition]. Vol Book 4. 2nd ed. Amsterdam, 1652.

025. Tulp N. Observationum medicarum libri tres [Three Books on Medical Observations]. Amsterdam: Ludovicum Elzevirum; 1641.

026. Bonet T. Sepulchretum sive anatomica practica [Burial or the practice of anatomy]. Chouette. 1679; Lib 2, sect. 7(obs. 155): 626.

027. Greiselius JG [Greisel]. De repentina suave morte ex pancreate sphacelato [On a rapid death from a necrosed pancreas]. Breslau, Poland: Academy of Natural History Breslau, 1681.

028. Morgagni GB. De sedibus et causis morborum per anatomen indagatis libri quinque [Fie books on the seats and causes of diseases as discovered by the anatomist]. Venice: Typographia Remondiniana, 1761.

029. Portal A. Cours d'Anatomie mé dicale ou Elémens de l'Anatomie de l'Homme [Course in medical anatomy or elements of human anatomy]. Vol V. Paris: Baudoin, 1803.

030. Gendrin AN. Histoire anatomique des inflammations [Anatomic history of inflammations]. Montpellier: Béchetjne & Gabon, 1826.

031. Andral G. Clinique Médicale, une choix d'observations recueillies à l'Hôpital de la charité, Clinique de M. Lerminier [Medical clinics, a selection of observations collected in the Charity Hospital, Clinic of Mr Lerminnier]. Paris/Brussels: Gabon and Montpellier, 1829-1833.

032. Fitz RH. Acute pancreatitis: a consideration of pancreatic hemorrhage, hemorrhagic, suppurative and gangrenous pancreatitis, and of disseminated fat necrosis. Boston Med Surg J 1889; 120: 181-8.

033. Harris FF. A case of diabetes mellitus quickly following mumps. Boston Med Surg J 1899; 140: 465-9.

034. Neumann KG. Von den Krankheiten des Menschen. 1. Teil oder allgemeine Pathologie [On the diseases of man. First part or general pathology]. Berlin: Herbig, 1829.

035. von Störck A. Handbuch für Heilkunde [Textbook of medicine]. Jena, Germany: Bielcke, 1799.

036. Shea J. Abscesses of the pancreas with large lumbricus obstructing the pancreas and the duodenum. Lancet 1881; 2: 791-2.

037. Lieutaud J. Historia anatamo-medica sistens numerosissima cadaverum humaniorum [Anatomico-pathological history based on the examination of numerous human corpses]. Paris: Portal, 1767.

038. Crampton P. (no title). Trans Coll Phys Ireland 1818; 2: 137.

039. Rokitansky K. Lehrbuch der pathologischen Anatomie [Textbook of pathologic anatomy]. Vol 3. Portal, Vienna: Braümuller, 1842.

040. Klebs AE. Handbuch der pathologischen anatomie [Handbook of pathologic anatomy]. Vol 3. Berlin: Hirschwald, 1870.

041. Cullen TS. A new sign in ruptured extra-uterine pregnancy. Am J Obstet 1918; 78: 457.

042. Gray-Turner G. Local discoloration of abdominal wall as a sign of acute pancreatitis. Br J Surg 1920; 7: 394-5.

043. Leach SD, Gorelick F, Modlin IM. Acute pancreatitis at its centenary – the contribution of Reginald Fitz. Ann Surg 1990; 212: 109-13.

044. Fitz RH. The symptomatology and diagnosis of diseases of the pancreas. Proc N Y Path Soc 1898; 43: 1-26.

045. Baillie M. A series of engravings accompanied with explanations which are intended to illustrate the morbid anatomy of some of the most important parts of the human body. London: Bulmer & Co, 1799.

046. Mayo Robson AW, Moynihan BGA. Diseases of the pancreas and their surgical treatment. Philadelphia/London: WB Saunders, 1902.

047. Mayo Robson AW, Cammidge PJ. The pancreas its surgery and pathology. Philadelphia/London: WB Saunders, 1907.

048. Comfort M, Gambill E, Baggesnstoss A. Chronic relapsing pancreatitis: a study of 29 cases without associated disease of the biliary or gastrointestinal tract. Gastroenterology 1946; 6: 238-76.

049. Senn N. The surgery of the pancreas. Trans Am Surg Assoc. 1886; 4: 99-225.

050. Chiari H. Über die Selbstverdauung des menschlichen Pankreas [On autodigestion of the human pancreas]. Z Helik 1896; 17: 1.

051. Moynihan B. Acute pancreatitis. Ann Surg. 1925; 81: 132-42.

052. Körte W. Die chirurgischen Krankheiten und Verletzungen des Pankreas [The surgical diseases and injuries of the pancreas]. Stuttgart: Enke, 1899.

053. Oser L. Die Erkrankungen des Pankreas [The diseases of the pancreas]. Vienna: Hölder, 1898.

054. Lancereaux E. Traité des malades du foie et du pancréas. Paris: Victor Masson et fils, 1899.

055. Opie EL. The relation of cholelithiasis to disease of the pancreas and to fat necrosis. Am J Med Sci 1901; 121: 27-43.

056. Opie EL. The etiology of acute hemorrhagic pancreatitis. Bull Johns Hopkins Hosp 1901; 12: 182-8.

057. Opie EL. Diseases of the pancreas: its cause and nature. Philadelphia/London: JB Lippincott Company, 1903.

058. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994; 330: 1198-1210.

059. Edmondson HA, Bullock WK, Mehl JW. Chronic pancreatitis and lithiasis; a clinicopathologic study of 62 cases of chronic pancreatitis. Am J Pathol 1949; 25: 1227-47.

060. Symmers WSC. Acute alcoholic pancreatitis. Dublin J Med Sci 1917; 143: 244-7.

061. Owens JL Jr, Howard JM. Pancreatic calcification: a late sequel in the natural history of chronic alcoholism and alcoholic pancreatitis. Ann Surg 1958; 147: 326-38.

062. Sarles H. Chronic calcifying pancreatitis-chronic alcoholic pancreatitis. Gastroenterology 1974; 66: 604-16.

063. Tiscornia OM, Palasciano G, Sarles H. Proceedings: pancreatic changes induced by chronic (two years) ethanol treatment in the dog. Gut 1974; 15: 839.

064. Renner IG, Savage WT, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. Dig Dis Sci 1985; 30: 1005-18.

065. Seligson U, Cho JW, Ihre T, Lundh G. Clinical course and autopsy findings in acute and chronic pancreatitis. Acta Chir Scand.1982; 148: 269-74.

066. Katz M, Carangelo R, Miller LJ, Gorelick F. Effect of ethanol on cholecystokinin-stimulated zymogen conversion in pancreatic acinar cells. Am J Physiol 1996; 270 (1 Pt 1):G171-5.

067. Pandol SJ, Periskic S, Gukovsky I, Zaninovic V, Jung Y, Zong Y, Solomon TE, Gukovskaya AS, Tsukamoto H. Ethanol diet increases the sensitivity of rats to pancreatitis induced by cholecystokinin octapeptide. Gastroenterology 1999; 117: 706-6.

068. Hanck C, Whitcomb DC. Alcoholic pancreatitis. Gastroenterol Clin North Am 2004; 33: 751-65.

069. Cameron JL, Capuzzi DM, Zuidema GD, Margolis S. Acute pancreatitis with hyperlipemia: the incidence of lipid abnormalities in acute pancreatitis. Ann Surg 1973; 177: 483-9.

070. Wohlgemuth J. Ueber eine neue Methode zur Bestimmung des diastatischen Fermentes [On a new method for the determination of the diastatic enzyme]. Biochem Zschr 1908; 9: 1.

071. Elman R, AN, Graham EA. Value of blood amylase estimations in the diagnosis of pancreatic disease: a clinical study. Arch Surg 1929; 19: 943-67.

072. O'Donnell MD, FitzGerald O, McGeeney KF. Differential serum amylase determination by use of an inhibitor, and design of a routine procedure. Clin Chem 1977; 23: 560-6.

073. Berk JE, Kizu H, Wilding P, Searcy RL. Macroamylasemia: a newly recognized cause for elevated serum amylase activity. N Engl J Med 1967; 277: 941-6.

074. Cherry LS, Crandall JA. Specificity of pancreatic lipase: its appearance in blood after pancreatic injury. Am J Physiol 1932; 100: 266.

075. Comfort MW. Serum lipase: its diagnostic value. Proc Staff Meeting Mayo Clin 1935; 10: 810.

076. Lankisch PG, Haseloff M, Becher R. No parallel between the biochemical course of acute pancreatitis and morphologic findings. Pancreas 1994; 9: 240-3.

077. Temler RS, Felber JP. Radioimmunoassay of human plasma trypsin. Biochim Biophys Acta 1976; 445: 720-8.

078. Temler RS, Felber JP. Radioimmunoassay of human plasma trypsin. Biochim Biophys Acta 1976; 445: 720-8.

079. Rinderknecht H, Geokas MC, Silverman P, Lillard Y, Haverback BJ. New methods for the determination of elastase. Clin Chim Acta 1968; 19: 327-39.

080. Geokas MC, Wollesen F, Rinderknecht H. Radioimmunoassay for pancreatic carboxypeptidase B in human serum. J Lab Clin Med 1974; 84: 574-83.

081. Frey CF. Classification of pancreatitis: state-of-the-art, 1986. Pancreas 1986; 1: 62-8.

082. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974; 139: 69-81.

083. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA. Objective early identification of severe acute pancreatitis. Am J Gastroenterol 1974; 61: 443-51.

084. Ranson JH. Diagnostic standards for acute pancreatitis. World J Surg 1997; 21: 136-42.

085. Sarles H. Proposal adpopted unanimously by the participants of the symposium on pancreatitis at Marseille, 1963. Bibl Gastroenterol 1965; 7: VII-VIII.

086. Sarles H. Definitions and classifications of pancreatitis. Pancreas 1991; 6: 470-4.

087. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993; 128: 586-90.

088. Balthazar EJ, Ranson JH, Naidich DP, Megibow AJ, Caccavale R, Cooper MM. Acute pancreatitis: prognostic value of CT. Radiology 1985; 156: 767-72.

089. McClusky DA, Skandalakis LJ, Colborn GL, Skandalakis JE. Harbinger or hermit? Pancreatic anatomy and surgery through the ages – part 3. World J Surg 2002; 26: 1512-24.

090. Paxton JR, Payne JH. Acute pancreatitis. Surg Gynecol Obstet 1948; 86: 69-75.

091. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery 1968; 64: 134-42.

092. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 2004; 328: 1407.

093. 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.

094. Konttinen YP. Epsilon-aminocaproic acid in treatment of acute pancreatitis. Scand J Gastroenterol 1971; 6: 715-8.

095. Uhl W, Büchler MW, Malfertheiner P, Beger HG, Adler G, Gaus W. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. Gut 1999; 45: 97-104.

096. Andriulli A, Leandro G, Clemente R, Festa V, Caruso N, Annese V, Lezzi G, Lichino E, Bruno F, Perri F. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. Aliment Pharmacol Ther 1998; 12: 237-45.

097. Classen M, Ossenberg FW, Wurbs D. Pancreatitis-an indication for endoscopic papillotomy. Endoscopy 1978; 10: 223 (abstract).

098. Safrany L, Cotton PB. A preliminary report: urgent duodenoscopic sphincterotomy for acute gallstone pancreatitis. Surgery 1981; 89: 424-8.

099. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet. 1988;2(8618):979-983.

100. Moss RW. The life and times of John Beard, DSc (1858-1924). Integr Cancer Ther 2008; 7: 229-51.

101. Moss RW. Enzymes, trophoblasts, and cancer: the afterlife of an idea (1924-2008). Integr Cancer Ther 2008; 7: 262-75.

102. Fernández-Zapico ME. Focus is key to becoming an expert in any field of research. An interview with Prof. Howard A. Reber, Chief of Gastrointestinal Surgery, and Director of the Ronald S. Hirshberg Pancreatic Cancer Research Laboratory, University of California Los Angeles (UCLA), Los Angeles, Calif., USA. Pancreatology 2009; 9: 197-9.

103. Fernández-Zapico ME. Keep at It! Accept the Challenges of Your Critics. An Interview with John M. Howard, MD, Professor Emeritus, Division of General Surgery, University of Toledo, Toledo, Ohio, USA. Pancreatology 2009; 9: 551-3.

104. Tanaka M, Shiratori K, Matsuno S, Go VLW. Memorial tribute to Katsusuke Satake, MD. Pancreatology 2009; 9: 977-8.

105. Docherty K. Pancreatic stellate cells can form new beta-like cells. Biochem J 2009; 412: e1-4.

106. Sanchez D, Mueller CM, Zenilman ME. Pancreatic regenerating gene I and acinar cell differentiation: influence on cellular lineage. Pancreas 2009; 38: 572-7.

107. Wandzioch E, Zaret KS. Dynamic signaling network for the specification of embryonic pancreas and liver progenitors. Science 2009; 324: 1707-10.

108. Pittenger GL, Taylor-Fishwick D, Vinik AI. The role of islet neogeneis-associated protein (INGAP) in pancreatic islet neogenesis. Curr Protein Pept Sci 2009; 10: 37-45.

109. Hamelin R, Allagnat F, Haefliger JA, Meda P. Connexins, diabetes and the metabolic syndrome. Curr Protein Pept Sci 2009; 10: 18-29.

110. Li Z, Korzh V, Gong Z. DTA-mediated targeted ablation revealed differential interdependence of endocrine cell lineages in early development of zebrafish pancreas. Differentiation 2009 2009; 78: 241-52.

111. Dorrell C, Abraham SL, Lanxon-Cookson KM, Canaday PS, Streeter PR, Grompe M. Isolation of major pancreatic cell types and long-term culture-initiating cells using novel human surface. Stem Cell Res 2008; 1: 183-94.
112. Fraker CA, Ricordi C, Inverardi L, Domínguez-Bendala J. Oxygen: a master regulator of pancreatic development? Biol Cell 2009; 101: 431-40.

113. Mulla C, Geras-Raaka E, Raaka BM, Gershengorn MC. High levels of thyrotropin-releasing hormone receptors activate programmed cell death in human pancreatic precursors. Pancreas 2009; 38: 197-202.

114. Kim JY, Lee JM, Kim KW, Park HS, Choi JY, Kim SH, Kim MA, Lee JY, Han JK, Choi BI. Ectopic pancreas: CT findings with emphasis on differentiation from small gastrointestinal stromal tumor and leiomyoma. Radiology 2009; 252: 92-100.

115. Volchok J, Massimi T, Wilkins S, Curletti E. Duodenal diverticulum: case report of a perforated extraluminal diverticulum containing ectopic pancreatic tissue. Arch Surg 2009; 144: 188-90.

116. Hashimoto Y, Ross AS, Traverso LW. Circumportal pancreas with retroportal main pancreatic duct. Pancreas 2009; 38: 713-5.

117. Ledinsky M, Suić I, Babić N, Kujundzić S. Symptoms of annular pancreas exacerbated by pregnancy. Acta Clin Croat 2009; 48: 47-50.

118. Sandrasegaran K, Patel A, Fogel EL, Zyromski NJ, Pitt HA. Annular pancreas in adults. Am J Roentgenol 2009; 193: 455-60.

119. Arena F, Impellizzeri P, Scalfari G, Antonuccio P, Montalto AS, Racchiusa S, Romeo C. An uncommon case of associate intrinsic and extrinsic stenosis of the duodenum in newborn. Pediatr Med Chir 2008; 30: 212-4.

120. Kim SW, Shin HC, Kim IY, Bae SB, Park JM. Duplication of the spleen with a short pancreas. Br J Radiol 2009; 82: e42-3.

121. Paraskevas G, Papaziogas B, Ioannidis O, Kitsoulis P, Spanidou S. Double common bile duct: a case report. Acta Chir Belg 2009; 109: 507-9.

122. Hac S, Nalecz A, Dobosz M, Reszetow J, Dobrowolski S, Friess H, Mihaljevic AL, Studniarek M, Jaskiewicz K, Sledzinski Z. Pancreatic duct diversity. Pancreas 2009; 38: 318-21.

123. Sakpal SV, Sexcius L, Babel N, Chamberlain RS. Agenesis of the dorsal pancreas and its association with pancreatic tumors. Pancreas 2009; 38: 367-73.

124. Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY, Son BK, Kim SH, Jo YJ, Park YS, Kim YS. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol 2009; 15: 1869-75.

125. Balli O, Karcaaltincaba M, Karaosmanoglu D, Akata D. Multidetector computed tomography diagnosis of fusion of pancreas and spleen confirmed by magnetic resonance imaging. J Comput Assist Tomogr 2009; 33: 291-2.

126. Toouli J. Sphincter of Oddi: function, dysfunction, and its management. J Gastroenteol Hepatol 2009; 24 suppl 3: S57-62.

127. Li CP, Qian W, Hou XH. Effect of four medications associated with gastrointestinal motility on Oddi sphincter in the rabbit. Pancreatology 2009; 9: 615-20.

128. Magni P, Dozio E, Ruscica M, Celotti F, Masini MA, Prato P, Broccoli M, Mambro A, Morè M, Strollo F. Feeding behavior in mammals including humans. Ann N Y Acad Sci 2009; 1163: 221-32.

129. García M, Hernández-Lorenzo P, San Román JI, Calvo JJ. Pancreatic duct secretion: experimental methods, ion transport mechanisms and regulation. Physiol Biochem 2008; 64: 243-57.

130. Rengman S, Weström B, Ahrén B, Pierzynowski SG. Arterial gastroduodenal infusion of cholecystokinin-33 stimulates the exocrine pancreatic enzyme release via an enteropancreatic reflex, without affecting the endocrine insulin secretion in pigs. Pancreas 2009; 38: 213-8.

131. Gullo L, Simoni P, Migliori M, Lucrezio L, Bassi M, Frau F, Lorenzo Costa P, Nesticò V. A study of pancreatic function among subjects over ninety years of age. Pancreatology 2009; 9: 240-4.

132. Boros LG, Deng QG, Pandol SJ, Tsukamoto H, Go VLW, Lee WNP. Ethanol diversely alters palmitate, stearate, and oleate metabolism in the liver and pancreas of rats using the deuterium oxide single tracer. Pancreas 2009; 38: e47-52.

133. Mishra R, Sellin D, Radovan D, Gohlke A, Winter R. Inhibiting islet amyloid polypeptide fibril formation by the red wine compound resveratrol. Chembiochem 2009; 10: 445-9.

134. Nauck MA. Unraveling the science of incretin biology. Am J Med 2009; 122 (6 suppl): S3-10.

135. Mudaliar S, Henry RR. Incretin therapies: effects beyond glycemic control. Am J Med 2009; 122 (6 suppl): S25-30.

136. Campbell RK. Type 2 diabetes: where we are today: an overview of disease burden, current treatments, and treatment strategies. J Am Pharm Assoc 2009; 49 suppl 1: S3-9.

137. Janosz KE, Zalesin KC, Miller WM, McCullough PA. Treating type 2 diabetes: incretin mimetics and enhancers. Ther Adv Cardiovasc Dis 2009; 3: 387-95.

138. White J. Efficacy and safety of incretin based therapies: clinical trial data. J Am Pharm Assoc 2009; 49 suppl 1: S30-40.

139. Nauck MA. Unraveling the science of incretin biology. Eur J Intern Med 2009; 20 (suppl 2): S303-8.

140. Mudaliar S, Henry RR. Incretin therapies: effects beyond glycemic control. Eur J Intern Med 2009: 20 (suppl 2): S319-28.

141. McCall MD, Toso C, Baetge EE, Shapiro AM. Are stem cells a cure for diabetes? Clin Sci 2009; 118: 87-97.

142. Foulis AK. Pancreatic pathology in type 1 diabetes in human. Novartis Found Symp 2008; 292: 2-13.

143. Brandhorst H, Friberg A, Andersson HH, Felldin M, Foss A, Salmela K, Lundgren T, Tibell A, Tufveson G, Korsgren O, Brandhorst D. The importance of tryptic-like activity in purified enzyme blends for efficient islet isolation. Transplantation 2009; 87: 370-5.

144. Lau J, Carlsson PO. Low revascularization of human islets when experimentally transplanted into the liver. Transplantation 2009; 87: 322-5.

145. Jha RK, Ma Q, Sha H, Palikhe M. Acute pancreatitis: a literature review. Med Sci Monit 2009; 15: RA 147-56.

146. Chan YC, Leung PS. Acute pancreatitis: animal models and recent advances in basic research. Pancreas 2007; 34: 1-14.

147. Bumbasirevic V, Radenkovic D, Jankovic Z, Karamarkovic A, Jovanovic B, Milic N, Palibrk I, Ivancevic N. Severe acute pancreatitis: overall and early versus late mortality in intensive care units. Pancreas 2009; 38: 122-5.

148. Mifkovic A, Skultety J, Pindak D, Pechan J. Specific aspects of acute pancreatitis. Bratisl Lek Listy 2009; 110: 544-52.

149. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 2009; 122: 333-4.

150. Lankisch PG, Karimi M, Bruns A, Maisonneuve P, Lowenfels AB. Temporal trends in incidence and severity of acute pancreatitis in Lüneburg County, Germany: a population-based study. Pancreatology 2009; 9: 420-6.

151. Barreto SG, Rodrigues J. Acute pancreatitis in Goa – a hospital-based study. J Indian Med Assoc 2008; 106: 575-6.

152. Sasajima K, Futami R, Matsutani T, Nomura T, Makino H, Maruyama H, Miyashita M. Increases in soluble tumor necrosis factor receptors coincide with increases in interleukin-6 and proteinases after major surgery. Hepatogastroenterology 2009; 56: 1377-81.

153. Botoi G, Andercou A. Interleukin 17 – prognostic marker of severe acute pancreatitis. Chirurgia 2009; 104: 431-8 (in Romanian).

154. Milnerowicz H, Jablonowska M, Bizon A. Change of zinc, copper, and metallothionein concentrations and the copper-zinc superoxide dismutase activity in patients with pancreatitis. Pancreas 2009: 38: 681-8.

155. Crawford MW, Pehora C, Lopez AV. Drug-induced acute pancreatitis in children receiving chemotherapy for acute leukemia: does propofol increase the risk? Anesth Analg 2009; 109: 379-81.

156. Tukiainen E, Kylanpaa ML, Repo H, Orpana A, Methuen T, Salaspuro M, Kemppainen E, Puolakkainen P. Hemostatic gene polymorphisms in severe acute pancreatitis. Pancreas 2009; 38: e43-6.

157. Thareja S, Bhardwaj P, Sateesh J, Saraya A. Variations in the levels of oxidative stress and antioxidants during early acute pancreatitis. Trop Gastroenterol 2009; 30: 26-31.

158. Wu BU, Johannes RS, Conwell DL, Banks PA. Early hemoconcentration predicts increased mortality only among transferred patients with acute pancreatitis. Pancreatology 2009; 9: 639-43.

159. Hjalmarsson C, Stenflo J, Borgström A. Activated protein C-protein C inhibitor complex, activation peptide of Carboxypeptidase B and C-reactive protein as predictors of severe acute pancreatitis. Pancreatology 2009; 9: 700-7.

160. Figueiredo FAF, Giovannini M, Monges G, Charfi S, Bories E, Pesenti C, Caillol F, Delpero JR. Pancreatic endocrine tumors: a large single-center experience. Pancreatology 2009; 9: 947-53.

161. Anderson F, Thomson SR, Clarke DL, Buccimazza I. Dyslipidaemic pancreatitis clinical assessment and analysis of disease severity and outcomes. Pancreatology 2009; 9: 252-7.

162. Deshpande AV, Thomas G, Shun A, Roy G, Stormon M, Gaskin K. Dominant dorsal duct syndrome: a rare cause of acute recurrent pancreatitis in children revisited. Pancreatology 2009; 9: 97-100.

163. Ryu JK. Evaluation of severity in acute pancreatitis. Korean J Gastroenterol 2009; 54: 205-11 (in Korean).

164. Gravante G, Garcea G, Ong SL, Metcalfe MS, Berry DP, Lloyd DM, Dennison AR. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. Pancreatology 2009; 9: 601-14.

165. Glisić T, Sijacki A, Vuković V, Subotić A. Bernard Organ Failure Score in estimation of most severe forms of acute pancreatitis. Srp Arh Celok Lek 2009; 137: 166-70 (in Serbian).

166. 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. Pancreatology 2009; 9: 41-6.

167. Vege SS, Gardner TB, Chari ST, Munukuti P, Pearson RK, Clain JE, Petersen BT, Baron TH, Farnell MB, Sarr MG. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include "moderately severe acute pancreatitis". Am J Gastroenterol 2009; 104: 710-5.

168. Wang X, Cui Z, Zhang J, Li HC, Zhang DP, Miao B, Cui YF, Zhao EP, Li ZG, Cui NQ. Early predictive factors of inhospital mortality in patients with severe acute pancreatitis. Pancreatology 2009; 9: 111-4 (letter).

169. Sharma A, Muddana V, Lamb J, Greer J, Papachristou GI, Whitcomb DC. Low serum adiponectin levels are associated with systemic organ failure in acute pancreatitis. Pancreas 2009; 38: 907-12.

170. Lindstrom O, Tukiainen E, Kylanpaa L, Mentula P, Rouhiainen A, Puolakkainen P, Rauvala H, Repo H. Circulating levels of a soluble form of receptor for advanced glycation end products and high-mobility group box chromosomal protein 1 in patients with acute pancreatitis. Pancreatology 2009; 9: e215-20.

171. Wu BU. The impact of hospital volume on outcomes in acute pancreatitis: a case for centers of excellence? Gastroenterology 2009; 137: 1886-8 (editorial).

172. Nguyen GC, Boudreau H, Jagannath SB. Hospital volume as a predictor for undergoing cholecystectomy after admission for acute biliary pancreatitis. Pancreatology 2009; 9: e42-7.

173. Bosmann M, Schreiner O, Galle PR. Coexistence of Cullen's and Grey Turner's signs in acute pancreatitis. Am J Med 2009; 122: 333-4.

174. Aysan E, Sevinc M, Basak E, Tardu A, Erturk T. Effectivity of qualitative urinary trypsinogen-2 measurement in the diagnosis of acute pancreatitis: a randomized, clinical study. Acta Chir Belg 2008; 108: 696-8.

175. Andersen AM, Novovic S, Ersboll AK, Jörgensen LN, Hansen MB. Urinary trypsinogen-2 dipstick in acute pancreatitis. Pancreatology 2009; 9: 26-30.

176. Yamamoto N, Matsumoto S, Komatsu H. A case of suspected acute pancreatitis after general anesthesia. Masui 2009; 58: 187-8 (in Japanese).

177. Coté GA, Gottstein JH, Daud A, Blei AT. The role of etiology in the hyperamylasemia of acute liver failure. Am J Gastroenterol 2009; 104: 592-7.

178. Gullo L, Lucrezio L, Calculli L, Salizzoni E, Coe M, Migliori M, Casadei R, Costa PL, Nestico V. Magnetic resonance cholangiopancreatography in asymptomatic pancreatic hyperenzymemia. Pancreas 2009; 38: 396-400.

179. Hardt PD, Mayer K, Ewald N. Exocrine pancreatic involvement in critically ill patients. Curr Opin Clin Nutr Metab Care 2009; 12: 168-74.

180. Pradeep K, Wig J, Panda NB, Prasad R. Dose-related effect of propofol on pancreatic enzymes and triglyceride levels in patients undergoing non-abdominal surgery. Anaesth Intensive Care 2009; 37: 27-31.

181. Sliwińska-Mossoń M, Milnerowicz H, Zuchniewicz A, Andrzejak R, Antonowicz-Juchniewicz J. Influence of tobacco smoking on amylase activity in serum persons occupational exposed to heavy metals. Przegl Lek 2008; 65: 495-7 (in Polish).

182. Chuang TY, Chao CL, Lin BJ, Lu SC. Gestational hyperlipidemic pancreatitis caused by type III hyperlipoproteinemia with apolipoprotein E2/E2 homozygote. Pancreas 2009; 38: 716-7.

183. Cole RP. Heparin treatment for severe hypertriglyceridemia in diabetic ketoacidosis. Arch Intern Med 2009; 169: 1439-41.

184. Radenkovic D, Bajec D, Ivancevic N, Milic N, Bumbasirevic V, Jeremic V, Djukic V, Stefanovic B, Stefanovic B, Milosevic-Zbutega G, Gregoric P. d-Dimer in acute pancreatitis: a new approach for an early assessment of organ failure. Pancreas 2009; 38: 655-60.

185. Ocampo C, Zandalazini H, Kohan G, Silva W, Szelagowsky C, Oria A. Computed tomographic prognostic factors for predicting local complications in patients with pancreatic necrosis. Pancreas 2009; 38: 137-42.

186. Shinya S, Sasaki T, Nakagawa Y, Guiquing Z, Yamamoto F, Yamashita Y. The efficacy of diffusion-weighted imaging for the detection and evaluation of acute pancreatitis. Hepatogastroenterology 2009; 56: 1407-10.

187. Kim YK, Kim CS, Han YM. Role of fat-suppressed T1-weighted magnetic resonance imaging in predicting severity and prognosis of acute pancreatitis: an intraindividual comparison with multidetector computed tomography. J Comput Assist Tomogr 2009; 33: 651-6.

188. Wilcox CM, Kilgore M. Cost minimization analysis comparing diagnostic strategies in unexplained pancreatitis. Pancreas 2009; 38: 117-21.
189. Mitura K, Romanczuk M. Ruptured ectopic pregnancy mimicking acute pancreatitis. Ginekol Pol 2009; 80: 383-5.

190. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an american pediatric tertiary care center: is greater awareness among physicians responsible? Pancreatology 2009; 9: 5-8.

191. Treepongkaruna S, Thongpak N, Pakakasama S, Pienvichit P, Sirachainan N, Hongeng S. Acute pancreatitis in children with acute lymphoblastic leukemia after chemotherapy. J Pediatr Hematol Oncol 2009; 31: 812-5.

192. Zhang X, Wu D, Jiang X. ICAM-1 and acute pancreatitis complicated by acute lung injury. JOP 2009; 10: 8-14.

193. Koseki H, Tsurumoto T, Osaki M, Shindo H. Multifocal osteonecrosis caused by traumatic pancreatitis in a child. A case report. J Bone Joint Surg Am 2009; 91: 2229-31.

194. D'Amore L, Venosi S, Gossetti F, Negro A, Vermeil V, Montemurro L, Negro P. Abdominal aortic aneurysm following acute pancreatitis. Ann Ital Chir 2008; 79: 367-9.

195. Pyun DK, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yang SK, Kim JH, Yoon SN. Two cases of colonic obstruction after acute pancreatitis. Korean J Gastroenterol 2009; 54: 180-5 (in Korean).

196. Park JH, Lee TH, Cheon SL, Sun JH, Choi IK, Kim YS, Choi YW, Kang YW. Severe acute liver and pancreas damage in anorexia nervosa. Korean J Gastroenterol 2009; 54: 257-60 (in Korean).

197. Sanjay P, Yeeting S, Whigham C, Judson HK, Kulli C, Polignano FM, Tait IS. Management guidelines for gallstone pancreatitis. Are the targets achievable? JOP 2009; 10: 43-7.

198. Ainsworth AP, Svendsen LB. Routinely performed endoscopic retrograde cholangiopancreatography should not be recommended for gallstone-induced acute pancreatitis. Ugeskr Laeger 2009; 171: 2566-8 (in Danish).

199. Nebiker CA, Frey DM, Hamel CT, Oertli D, Kettelhack C. Early versus delayed cholecystectomy in patients with biliary acute pancreatitis. Surgery 2009; 145: 260-4.

200. Manes G, Di Giorgio P, Repici A, Macarri G, Ardizzone S, Porro GB. An analysis of the factors associated with the development of complications in patients undergoing precut sphincterotomy: a prospective, controlled, randomized, multicenter study. Am J Gastroenterol 2009; 104: 2412-7.

201. van Santvoort HC, Besselink MG, de Vries AC, Boermeester MA, Fischer K, Bollen TL, Cirkel GA, Schaapherder AF, Nieuwenhuijs VB, van Goor H, Dejong CH, van Eijck CH, Witteman BJ, Weusten BL, van Laarhoven CJ, Wahab PJ, Tan AC, Schwartz MP, van der Harst E, Cuesta MA, Siersema PD, Gooszen HG, van Erpecum KJ; Dutch Acute Pancreatitis Study Group. Collaborators (41): van Ramshorst B, Timmer R, Brink MA, Mundt M, Frankhuisen R, Consten EC, Nooteboom A, Jansen JB, Bongaerts GT, Buscher HC, Rosman C, Ootes L, Houben B, Ahmed Ali U, Zeguers V, Roeterdink A, Rijnhart HG, van Leeuwen MS, Haasnoot A, Rutten JP, van Dam R, Drixler TA, Spillenaar Bilgen EJ, van Embden P, van Ruler O, Gouma DJ, Bruno MJ, Hofker HS, Ploeg RJ, Kruijt Spanjer MR, Buitenhuis HT, van Vliet SU, Ramcharan S, Lange JF, Wijffels NA, van Walraven LA, Kubben FJ, van der Wal BC, van 't Hof G, Kuipers EJ, Poley JW. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 2009; 250: 68-75.

202. Brauer BC, Chen YK, Fukami N, Shah RJ. Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video). Gastrointest Endosc 2009; 70: 471-9.

203. Horakova M, Vadovicova I, Katuscak I, Janik J, Makovnik P, Sadlonova J. Consideration of endoscopic retrograde cholangiopancreatography in cases of acute biliary pancreatitis. Bratisl Lek Listy 2009; 110: 553-8.

204. Sandzén B, Haapamäki MM, Nilsson E, Stenlund HC, Oman M. Cholecystectomy and sphincterotomy in patients with mild acute biliary pancreatitis in Sweden 1988-2003: a nationwide register study. BMC Gastroenterol 2009; 9: 80.

205. Egea Valenzuela J, Belchí Segura E, Sánchez Torres A, Carballo Alvarez F. Acute pancreatitis associated with hypercalcemia. A report of two cases. Rev Esp Enferm Dig 2009; 101: 65-9.

206. Phatak UP, Park AJ, Latif SU, Bultron G, Pashankar DS, Husain SZ. Recurrent acute pancreatitis in a child with primary hyperparathyroidism. J Pediatr Endocrinol Metab 2008; 21: 1191-4.

207. Benedetti A, Parent ME, Siemiatycki J. Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: results from a case-control study in Montreal. Cancer Detect Prev 2009; 32: 352-62.

208. Pongprasobchai S, Thamcharoen R, Manatsathit S. Changing of the etiology of acute pancreatitis after using a systematic search. J Med Assoc Thai 2009; 92 Suppl 2: S38-42.

209. Nordback I, Pelli H, Lappalainen-Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology 2009; 136: 848-55.

210. Pelli H, Lappalainen-Lehto R, Piironen A, Järvinen S, Sand J, Nordback I. Pancreatic damage after the first episode of acute alcoholic pancreatitis and its association with the later recurrence rate. Pancreatology 2009; 9: 245-51.

211. Martinez-Torres H, Rodriguez-Lomeli X, Davalos-Cobian C, Garcia-Correa J, Maldonado-Martinez JM, Medrano-Muñoz F, Fuentes-Orozco C, Gonzalez-Ojeda A. Oral allopurinol to prevent hyperamylasemia and acute pancreatitis after endoscopic retrograde cholangiopancreatography. World J Gastroenterol 2009; 15: 1600-6.

212. Matsushita M, Takakuwa H, Shimeno N, Uchida K, Nishio A, Okazaki K. Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis. J Gastroenterol 2009; 44: 71-5.

213. Sherman S, Cheng CL, Costamagna G, Binmoeller KF, Puespoek A, Aithal GP, Kozarek RA, Chen YK, Van Steenbergen W, Tenner S, Freeman M, Monroe P, Geffner M, Deviere J. Efficacy of recombinant human interleukin-10 in prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in subjects with increased risk. Pancreas 2009; 38: 267-74.

214. Bai Y, Gao F, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: a meta-analysis. Pancreas 2009; 38: 126-30.

215. Bai Y, Gao F, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: a meta-analysis. Pancreas 2009; 38: 126-30.

216. Pezzilli R, Mariani A, Gabbrielli A, Morselli-Labate AM, Barassi A. Serum and urine trypsinogen activation peptide in assessing post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreatology 2009; 9: 108-9 (letter).

217. Mast JJ, Morak MJ, Brett BT, van Eijck CH. Ischemic acute necrotizing pancreatitis in a marathon runner. JOP 2009; 10: 53-4.

218. Sasaki Y, Aoki S, Aoki K, Achiwa K, Yama T, Kubota M, Ishikawa D, Mizutani T, Kunii S, Watanabe K, Okumura A. Acute pancreatitis associated with the administration of ceftriaxone in an adult patient. Nippon Shokakibyo Gakkai Zasshi 2009; 106: 569-75 (in Japanese).

219. Lee KH, Shelat VG, Low HC, Ho KY, Diddapur RK. Recurrent pancreatitis secondary to pancreatic ascariasis. Singapore Med J 2009; 50: 218-9.

220. Turkulov V, Madle-Samardzija N, Canak G, Gavrancić C, Vukadinov J, Doder R. Various clinical manifestations of brucellosis infektion. Med Pregl 2008; 61: 517-20 (in Serbian).

221. Baburaj P, Antony T, Louis F, Harikrishnan BL. Acute abdomen due to acute pancreatitis - a rare presentation of leptospirosis. Assoc Physicians India 2008; 56: 911-2.

222. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. Br J Surg 2009; 96: 1243-52.

223. Hen K, Bogdański P, Pupek-Musialik D. Successful treatment of severe hypertriglyceridemia with plasmapheresis – case report. Pol Merkur Lekarski 2009; 26: 62-4 (in Polish).

224. Ishikawa T, Imai M, Kamimura H, Ushiki T, Tsuchiya A, Togashi T, Watanabe K, Seki K, Ohta H, Yoshida T, Kamimura T. Therapeutic efficacy of continuous arterial infusion of the protease inhibitor and the antibiotics and via celiac and superior mesenteric artery for severe acute pancreatitis – pilot study. Hepatogastroenterology 2009; 56: 524-8.

225. Yang C, Guanghua F, Wei Z, Zhong J, Penghui J, Xin F, Xiping Z. Combination of hemofiltration and peritoneal dialysis in the treatment of severe acute pancreatitis. Pancreatology 2009; 9: 16-9.

226. Botoi G, Andercou A. Early and prolonged peritoneal lavage with laparoscopy in severe acute pancreatitis. Chirurgia 2009; 104: 49-53 (in Romanian).

227. Besselink MG, van Santvoort HC, Boermeester MA, Nieuwenhuijs VB, van Goor H, Dejong CH, Schaapherder AF, Gooszen HG; Dutch Acute Pancreatitis Study Group.Collaborators (53). Timing and impact of infections in acute pancreatitis. Br J Surg 2009; 96: 267-73.

228. Besselink MG, van Santvoort HC, Renooij W, de Smet MB, Boermeester MA, Fischer K, Timmerman HM, Ahmed Ali U, Cirkel GA, Bollen TL, van Ramshorst B, Schaapherder AF, Witteman BJ, Ploeg RJ, van Goor H, van Laarhoven CJ, Tan AC, Brink MA, van der Harst E, Wahab PJ, van Eijck CH, Dejong CH, van Erpecum KJ, Akkermans LM, Gooszen HG; Dutch Acute Pancreatitis Study Group. Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. Ann Surg 2009; 250: 712-9.

229. Koretz RL. Probiotics, critical illness, and methodologic bias. Nutr Clin Pract 2009; 24: 45-9.

230. Marusić S, Sićaja M, Kujundzić M, Banić M, Jaksić O, Vrazić H. The utilization of antibiotics in the management of acute pancreatitis – experience from one transitional country university hospital. Coll Antropol 2008; 32: 1189-94.

231. Navaneethan U, Vege SS, Chari ST, Baron TH. Minimally invasive techniques in pancreatic necrosis. Pancreatology 2009; 9: 867-75.

232. Becker V, Huber W, Meining A, Prinz A, Umgelter A, Ludwig L, Bajbouj M, Gaa J, Schmid RM. Infected necrosis in severe pancreatitis – combined nonsurgical multi-drainage with directed transabdominal high-volume lavage in critically ill patients. Pancreatology 2009; 9: 280-6.

233. Babu BI, Siriwardena AK. Practical strategies for case selection in minimally invasive necrosectomy. Pancreatology 2009; 9: 9-12.

234. Hasibeder WR, Torgersen C, Rieger M, Dünser M. Critical care of the patient with acute pancreatitis. Anaesth Intensive Care 2009; 37: 190-206.

235. Kvinlaug K, Kriegler S, Moser M. Emphysematous pancreatitis: a less aggressive form of infected pancreatic necrosis? Pancreas 2009; 38: 667-71.

236. Neri V, Ambrosi A, Fersini A, Tartaglia N, Valentino TP. Minimally invasive treatment of acute intrahepatic fluid collections with acute biliary pancreatitis. JSLS 2009; 13: 269-72.

237. Coelho D, Ardengh JC, Eulálio JM, Manso JE, Mönkemüller K, Coelho JF. Management of infected and sterile pancreatic necrosis by programmed endoscopic necrosectomy. Dig Dis 2008; 26: 364-9.

238. Prochazka V, Al-Eryani S, Herman M. Endoscopic treatment of multiple pancreatic abscesses case report and review of the literature. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2009; 153: 27-30.

239. Rocha FG, Benoit E, Zinner MJ, Whang EE, Banks PA, Ashley SW, Mortele KJ. Impact of radiologic intervention on mortality in necrotizing pancreatitis: the role of organ failure. Arch Surg 2009; 144: 261-5.

240. Pezzilli R, Morselli-Labate AM, Campana D, Casadei R, Brocchi E, Corinaldesi R. Evaluation of patient-reported outcome in subjects treated medically for acute pancreatitis: a follow-up study. Pancreatology 2009; 9: 375-82.

241. Jha RK, Ma Q, Sha H, Palikhe M. Protective effect of resveratrol in severe acute pancreatitis-induced brain injury. Pancreas 2009; 38: 947-53.

242. Kilian M, Gregor JI, Heukamp I, Wagner C, Walz KM, Schimke I, Kristiansen G, Wenger FA. Early inhibition of prostaglandin synthesis by n-3 fatty acids determinates histologic severity of necrotizing pancreatitis. Pancreas 2009; 38: 436-41.

243. Yuan H, Jin X, Sun JB, Li F, Feng Q, Zhang CQ, Cao Y, Wang Y. Protective effect of HMGB1 A Box on organ injury of acute pancreatitis in mice. Pancreas 2009; 38: 143-8.

244. Mann O, Tiefenbacher WJ, Kaifi J, Schneider C, Kluth D, Bloechle C, Yekebas E, Izbicki JR, Strate T. Effect of platelet-activating factor antagonist WEB 2086 on microcirculatory disorders in acute experimental pancreatitis of graded severity. Pancreas 2009; 86: 58-64.

245. Wang LW, Li ZS, Li S, Jin ZD, Zou, Duo W, Chen F. Prevalence and clinical features of chronic pancreatitis in China: a retrospective multicenter analysis over 10 years. Pancreas 2009; 38: 248-54.

246. Bhasin DK, Singh G, Rana SS, Chowdry SM, Shafiq N, Malhotra S, Sinha SK. Clinical profile of idiopathic chronic pancreatitis in North India. Clin Gastroenterol Hepatol 2009; 7: 594-9.

247. Díte P, Novotný I, Precechtelová M, Růzicka M, Záková A, Trna J, Hermannová M, Sevcíková A. Incidence of pancreatic carcinoma in persons with chronic pancreatitis. Vnitr Lek 2009; 55: 18-21 (in Czech).

248. Aoyagi H, Okada T, Hasatani K, Mibayashi H, Hayashi Y, Tsuji S, Kaneko Y, Yamagishi M. Impact of cystic fibrosis transmembrane conductance regulator gene mutation on the occurrence of chronic pancreatitis in Japanese patients. J Int Med Res 2009; 37: 378-84.

249. Chang MC, Chang YT, Wei SC, Liang PC, Jan IS, Su YN, Kuo CH, Wong JM. Association of novel chymotrypsin C gene variations and haplotypes in patients with chronic pancreatitis in Chinese in Taiwan. Pancreatology 2009; 9: 287-92.

250. Mora J, Comas L , Ripoll E, Gonçalves P, Queraltó J, González-Sastre F, Farré A. Genetic mutations in a Spanish population with chronic pancreatitis. Pancreatology 2009; 9: 644-51.

251. Diaconu B. Risk factors in chronic pancreatitis. Rom J Intern Med 2009; 47: 3-8.

252. Girish BN, Vaidyanathan K, Ananth Rao N, Rajesh G, Reshmi S, Balakrishnan V. Chronic pancreatitis is associated with hyperhomocysteinemia and derangements in transsulfuration and transmethylation pathways. Pancreatology 2009; 9: e11-6.

253. Vinokurova LV, Drozdov VN, Tkachenko EV, Trubitsyna IE, Varvanina GG. Etiology and pathogenesis of duodenal mucosa lesion in chronic pancreatitis. Ter Arkh 2009; 81: 65-8 (in Russian).

254. Schrader H, Menge B, Belyaev O, Uhl W, Schmidt WE, Meier JJ. Amino acid malnutrition in patients with chronic pancreatitis and pancreatic carcinoma- Pancreas 2009; 38: 416-21.

255. Madarasingha NP, Satgurunathan K, Fernando R. Pancreatic panniculitis: A rare form of panniculitis. Dermatol Online J 2009; 15: 17.

256. Bhutani MS, Arantes V, Verma D, Moezzi J, Suryaprasad S, Kapadia AS, Gopalswamy N. Histopathologic correlation of endoscopic ultrasound findings of chronic pancreatitis in human autopsies. Pancreas 2009; 38: 820-4.

258. Gardner TB, Janec EM, Gordon SR. Relationship between patient symptoms and endosonographic findings in chronic pancreatitis. Pancreatology 2009; 9: 398-403.

259. Vegting IL, Tabbers MM, Taminiau JA, Aronson DC, Benninga MA, Rauws EA. Is endoscopic retrograde cholangiopancreatography valuable and safe in children of all ages? J Peditr Gastroenterol Nutr 2009; 48: 66-71.

260. Nakamura H, Morifuji M, Murakami Y, Uemura K, Ohge H, Hayashidani Y, Sudo T, Sueda T. Usefulness of a 13C-labeled mixed triglyceride breath test for assessing pancreatic exocrine function after pancreatic surgery. Surgery 2009; 145: 168-75.

261. Andrea P, Andreas DW, Marc B, Katharina H, Michael T, Michael B, Klaus P, Ansgar LW. Pancreas and liver injury are associated in individuals with increased alcohol consumption. Clin Gastroenterol Hepatol 2009 Jun 25 [Epub ahead of print].

262. Tsujimoto T, Kawaratani H, Yoshiji H, Uemura M, Fukui H. Recent developments in the treatment of alcoholic chronic pancreatitis. Curr Drug Abuse Rev 2008; 1: 197-202.

263. Pelli H, Sand J, Nordback I. Can the recurrence of alcohol-induced pancreatitis be prevented? Duodecim 2009; 125: 1195-200 (in Finnish).

264. Levenick JM, Gordon SR, Sutton JE, Suriawinata A, Gardner TB. A comprehensive, case-based review of groove pancreatitis. Pancreas 2009; 38: e169-75.

265. Mullhaupt B, Ammann RW. Total pancreatectomy for intractable pain in chronic pancreatitis? Pancreatology 2009; 9: 110-1 (letter).

266. Pongprasobchai S, Manatsathit S. Natural course of abdominal pain in chronic pancreatitis with intermittent (type A) pain after conservative treatment. J Med Assoc Thai 2009; 92 (suppl 2): S43-8.

267. Ceyhan GO, Deucker S, Demir IE, Erkan M, Schmelz M, Bergmann F, Müller MW, Giese T, Büchler MW, Giese NA, Friess H. Neural fractalkine expression is closely linked to pain and pancreatic neuritis in human chronic pancreatitis. Lab Invest 2009; 89: 347-61.

268. Kongkam P, Wagner DL, Sherman S, Fogel EL, Whittaker SC, Watkins JL, McHenry L, Lehman GA. Intrathecal narcotic infusion pumps for intractable pain of chronic pancreatitis: a pilot series. Am J Gastroenterol 2009; 104: 1249-55.

269. Winstead NC, Wilcox CM. Clinical trials of pancreatic enzyme replacement for painful chronic pancreatitis – a review. Pancreatology 2009; 9: 344-50.

270. Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, Longo L, D'Orazio C. Efficacy and tolerability of Creon for children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas 2009; 38: 693-9.

271. Hill JS, McPhee JT, Whalen GF, Sullivan ME, Warshaw AL, Tseng JF. In-hospital mortality after pancreatic resection for chronic pancreatitis: population-based estimates from the nationwide inpatient sample. J Am Coll Surg 2009; 209: 468-76.

272. Das MK, Roy H, Afaque Y, Mukherjee A, Gautam D. Pancreaticogastrostomy in cases of chronic pancreatitis: a preliminary study. J Indian Med Assoc 2008; 106: 797-8.

273. Pakosz-Golanowsha M, Post M, Lubikowski J, Butkiewicz J, Białek A, Raszeja-Wyszomirska J, Wiechowska-Kozłowska A, Milkiewicz P, Wójcicki M. Partington-Rochelle pancreaticojejunostomy for chronic pancreatitis: analysis of outcome including quality of life. Hepatogastroenterology 2009; 56: 1533-7.

274. Niclauss N, Morel P, Volonte F, Bosco D, Berney T. Pancreas and islets of Langerhans transplantation: current status in 2009 and perspectives. Rev Med Suisse 2009; 5: 1266-70 (in French).

275. Kobayashi T, Manivel JC, Bellin MD, Carlson AM, Moran A, Freeman ML, Hering BJ, Sutherland D. Correlation of pancreatic histopathologic findings and islet yield in children with chronic pancreatitis undergoing total pancreatectomy and islet autotransplantation. Pancreatology 2009; 9: 57-63.

276. Berman A, Pawelec K, Fiedor P. Allogeneic transplantation of isolated islet cells in clinical practice. Pol Arch Med Wewn 2009; 119: 326-32.

277. Garcea G, Weaver J, Phillips J, Pollard CA, Ilouz SC, Webb MA, Dennison AR. Total pancreatectomy with and without islet cell transplantation for chronic pancreatitis: a series of 85 consecutive patients. Pancreatology 2009; 38: e1-7.

278. Sauer BG, Gurka MJ, Ellen K, Shami V, Kahaleh M. Effect of pancreatic duct stent diameter on hospitalization in chronic pancreatitis: does size matter? Pancreatology 2009; 9: 728-31.

279. Borak GD, Romagnuolo J, Alsolaiman M, Holt EW, Cotton PB. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreas 2009; 38: 903-6.

280. Sauer BG, Gurka MJ, Ellen K, Shami VM, Kahaleh M. Effect of pancreatic duct stent diameter on hospitalization in chronic pancreatitis: does size matter? Pancreas 2009; 38: 728-31.

281. Khanna S, Tandon RK. Endotherapy for pain in chronic pancreatitis. J Gastroenterol Hepatol 2008; 23: 1649-56.

282. Jamry A. Proximal migration of pancreatic "pig tail" stent - a case report. Pol Merkur Lekarski 2009; 26: 127-30 (in Polish).

283. Sahai AV, Lemelin V, Lam E, Paquin SC. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. Am J Gastroenterol 2009; 104: 326-9.

284. Guarner L, Navalpotro B, Molero X, Giralt J, Malagelada JR. Management of painful chronic pancreatitis with single-dose radiotherapy. Am J Gastroenterol 2009; 104: 349-55.

285. Zion O, Genin O, Kawada N, Yoshizato K, Roffe S, Nagler A, Iovanna JL, Halevy O, Pines M. Inhibition of transforming growth factor-beta signaling by halofuginone as a modality for pancreas fibrosis prevention. Pancreas 2009; 38: 427-35.

286. Ali T, Srinivasan N, Le V, Chimpiri AR, Tierney WM. Pancreaticopleural fistula. Pancreas 2009; 38: e26-31.

287. Pezzilli R. Chronic pancreatitis: maldigestion, intestinal ecology and intestinal inflammation. World J Gastroenterol 2009; 15: 1673-6.

288. Lordan JT, Phillips M, Chun JY, Worthington TR, Menezes NN, Lightwood R, Hussain F, Tibbs C, Karanjia ND. A safe, effective, and cheap method of achieving pancreatic rest in patients with chronic pancreatitis with refractory symptoms and malnutrition. Pancreas 2009; 38: 689-92.

289. Huguet A, Savary G, Bobillier E, Le Huerou-Luron I. Defatted bovine colostrum-supplemented diet around weaning improves exocrine pancreatic secretion by means of volume, digestive enzymes, and antibacterial activity. Pancreas 2009; 38; 303-8.

290. Czakó L, Hegyi P, Rakonczay Z, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. Pancreatology 2009; 9: 351-9.

291. Ewald N, Raspe A, Kaufmann C, Bretzel RG, Kloer HU, Hardt PD. Determinants of exocrine pancreatic function as measured by fecal elastase-1 concentrations (FEC) in patients with diabetes mellitus. Eur J Med Res 2009; 14: 118-22.

292. Borak GD, Romagnuolo J, Alsolaiman M, Holt EW, Cotton PB. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreatology 2009; 9: 903-6.

293. Apte M, Pirola R, Wilson J. New insights into alcoholic pancreatitis and pancreatic cancer. J Gastroenterol Hepatol 2009; 24 suppl 3: S51-6.

294. Maydeo A, Bhandari S, Bapat M. Endoscopic balloon sphincteroplasty for extraction of large radiolucent pancreatic duct stones. Gastrointest Endosc 2009; 70: 798-802.

295. Dubova EA, Shchegolev AI. Duodenal dystrophy. Arkh Patol 2009; 71: 47-50 (in Russian).

296. Galloro G, Napolitano V, Magno L, Diamantis G, Pastore A, Mosella F, Donisi M, Ruggiero S, Pascariello A, Bruno M, Persico G. Pancreaticoduodenectomy as the primary therapeutic choice in cystic dystrophy of the duodenal wall in heterotopic pancreas. Chir Ital 2008; 60: 835-41.

297. Jonsdottir B, Bergsteinsson H, Baldursson O. Cystic fibrosis – review. Laekna bladid 2008; 94: 831-7 (in Icelandic).

298. Bodily KD, Takahashi N, Fletcher JG, Fidler JL, Hough DM, Kawashima A, Chari ST. Autoimmune pancreatitis: pancreatic and extrapancreatic imaging findings. Am J Roentgenol 2009; 192: 431-7

299. Choi EK, Kim MH, Jang SJ, Lee KH, Hwang CY, Moon SH, Lee TY, Koh CO, Park DH, Lee SS, Seo DW, Lee SK. Differences in pancreatic immunohistochemical staining profiles of TGF-beta1, MMP-2, and TIMP-2 between autoimmune and alcoholic chronic pancreatitis. Pancreas 2009; 38: 739-45.

300. Yamamoto H, Yamaguchi H, Aishima S, Oda Y, Kohashi K, Oshiro Y, Tsuneyoshi M. Inflammatory myofibroblastic tumor versus IgG4-related sclerosing disease and inflammatory pseudotumor: a comparative clinicopathologic study. Am J Surg Pathol 2009; 33: 1330-40.

301. Chang MC, Chang YT, Wei SC, Kuo CH, Liang PC, Wong JM. Autoimmune pancreatitis associated with high prevalence of gastric ulcer independent of helicobacter pylori infection status. Pancreas 2009; 38: 442-6.

302. Wang Q, Lu CM, Guo T, Qian JM. Eosinophilia associated with chronic pancreatitis. Pancreas 2009; 38: 149-53.

303. Okazaki K, Kawa S, Kamisawa T, Ito T, Inui K, Irie H, Irisawa A, Kubo K, Notohara K, Hasebe O, Fujinaga Y, Ohara H, Tanaka S, Nishino T, Nishimori I, Nishiyama T, Suda K, Shiratori K, Shimosegawa T, Tanaka M. Japanese clinical guidelines for autoimmune pancreatitis. Pancreatology 2009; 9: 849-66.

304. Chari ST, Longnecker DS, Klöppel G. The diagnosis of autoimmune pancreatitis: a western perspective. Pancreatology 2009; 9: 846-8.

305. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. N Eng J Med 2009; 361: 2135-42.

306. Kamisawa T, Tsuruta K, Okamoto A, Horiguchi SI, Hayashi Y, Yun QX, Yamaguchi T, Sasaki T. Frequent and significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. Pancreatology 2009; 9: 890-5.

307. Choi EK, Kim MH, Jang SJ, Lee KH, Hwang CY, Moon SH, Lee TY, Koh CO, Park DH, Lee SS, Seo DW, Lee SK. Differences in pancreatic immunohistochemical staining profiles of TGF-beta1, MMP-2, and TIMP-2 between autoimmune and alcoholic chronic pancreatitis. Pancreatology 2009; 9: 739-45.

308. 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. Pancreatology 2009; 9: e1-5.

309. 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. Pancreatology 2009; 9: e6-10.

310. Itoh S, Nagasaka T, Suzuki K, Satake H, Ota T, Naganawa S. Lymphoplasmacytic sclerosing cholangitis: assessment of clinical, CT, and pathological findings. Clin Radiol 2009; 64: 1104-14.

311. Onishi T, Igarashi T, Ichikawa T. Case of retroperitoneal fibrosis after surgical treatment of autoimmune pancreatitis. Hinyokika Kiyo 2009; 55: 551-4 (in Japanese).

312. Moerkercke WV, Verhamme M, Meeus G, Oyen R, Steenbergen WV. A case of IgG4-related sclerosing disease with retroperitoneal fibrosis, autoimmune pancreatitis and bilateral focal nephritis. Pancreatology 2009; 9: 825-32.

313. Chang WI, Kim BJ, Lee JK, Kang P, Lee KH, Lee KT, Rhee JC, Jang KT, Choi SH, Choi CW, Choi DI, Lim JH. The clinical and radiological characteristics of focal mass-forming autoimmune pancreatitis: comparison with chronic pancreatitis and pancreatic cancer. Pancreas 2009; 38: 401-8.

314. Takahashi N, Fletcher JG, Hough DM, Fidler JL, Kawashima A, Mandrekar JN, Chari ST. Autoimmune pancreatitis: differentiation from pancreatic carcinoma and normal pancreas on the basis of enhancement characteristics at dual-phase CT. Am J Roentgenol 2009; 193: 479-84.

315. Lee TY, Kim MH, Park do H, Seo DW, Lee SK, Kim JS, Lee KT. Utility of 18F-FDG PET/CT for differentiation of autoimmune pancreatitis with atypical pancreatic imaging findings from pancreatic cancer. Am J Roentgenol 2009; 193: 343-8.

316. Matsubayashi H, Furukawa H, Maeda A, Matsunaga K, Kanemoto H, Uesaka K, Fukutomi A, Ono H. Usefulness of positron emission tomography in the evaluation of distribution and activity of systemic lesions associated with autoimmune pancreatitis. Pancreatology 2009; 9: 694-9.

317. Gardner TB, Levy MJ, Takahashi N, Smyrk TC, Chari ST. Misdiagnosis of autoimmune pancreatitis: a caution to clinicians. Am J Gastroenterol 2009; 104: 1620-3.

318. Motosugi U, Ichikawa T, Yamaguchi H, Nakazawa T, Katoh R, Itakura J, Fujii H, Sato T, Araki T, Shimizu M. Small invasive ductal adenocarcinoma of the pancreas associated with lymphoplasmacytic sclerosing pancreatitis. Pathol Int 2009; 59: 744-7.

319. Chan SK, Cheuk W, Chan KT, Chan JK. IgG4-related sclerosing pachymeningitis: a previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. Am J Surg Pathol 2009 ; 33: 1249-52.

320. Schorr F, Riemann JF. Pancreas duct stenosis of unknown origon. Dtsch Med Wochenschr 2009; 134: 477-80 (in German).

321. Romero M, Pérez-Grueso MJ, Repiso A, de la Cruz G, García Vela A, Martín Escobedo R, González de Frutos C, Carrobles JM. Autoimmune pancreatitis associated with retroperitoneal fibrosis: outcome after 24 months of follow-up. Rev Esp Enferm Dig 2008; 100: 648-51 (in Spanish).

322. Rebours V, Boutron-Ruault MC, Jooste V, Bouvier AM, Hammel P, Ruszniewski P, Lévy P. Mortality rate and risk factors in patients with hereditary pancreatitis: uni- and multidimensional analyses. Am J Gastroenterol 2009; 104:2312-7.

323. Diaconu BL, Ciobanu L, Mocan T, Pfützer RH, Scafaru MP, Acalovschi M, Singer MV, Schneider A. Investigation of the SPINK1 N34S mutation in Romanian patients with alcoholic chronic pancreatitis. A clinical analysis based on the criteria of the M-ANNHEIM classification. J Gastrointestin Liver Dis 2009; 18: 143-50.

324. Oh HC, Kim MH, Choi KS, Moon SH, Park DH, Lee SS, Seo DW, Lee SK, Yoo HW, Kim GH. Analysis of PRSS1 and SPINK1 mutations in Korean patients with idiopathic and familial pancreatitis. Pancreas 2009; 38: 180-3.

325. Suga K, Kawakami Y, Hiyama A, Hori K, Takeuchi M. F-18 FDG PET-CT findings in Mikulicz disease and systemic involvement of IgG4-related lesions. Clin Nucl Med 2009; 34: 164-7.

326. Hruban RH, Adsay NV. Molecular classification of neoplasms of the pancreas. Hum Pathol 2009; 40: 612-23.

327. Bradley E. Long-term survival after pancreatoduodenectomy for ductal adenocarcinoma: the emperor has no clothes? Pancreas 2008; 37: 349-51.

328. Fitzgerald TL, Bradley CJ, Dahman B, Zervos EE. Gastrointestinal malignancies: when does race matter? J Am Coll Surg 2009; 209: 645-52.

329. Hiripi E, Lorenzo Bermejo J, Li X, Sundquist J, Hemminki K. Familial association of pancreatic cancer with other malignancies in Swedish families. Br J Cancer 2009; 101: 1792-7.

330. Teiblum S, Thygesen LC, Johansen C. Sixty-one years of pancreatic cancer in Denmark from 1943 to 2003: a nationwide study. Pancreas 2009; 38: 374-8.

331. Guérin S, Doyon F, Hill C. The frequency of cancer in France in 2006, mortality trends since 1950, incidence trends since 1980 and analysis of the discrepancies between these trends. Bull Cancer 2009; 96: 51-7 (in French).

332. Bae JM. Explaining cancer incidence in the Jejudo population. J Prev Med Public Health 2009; 42: 67-72 (in Korean).

333. Louchini R, Beaupré M. Cancer incidence and mortality among Aboriginal people living on reserves and northern villages in Quebec, 1988-2004. Int J Circumpolar Health 2008; 67: 445-51.

334. Vaktskjold A, Ungurjanu TN, Klestsjinov NM. Cancer incidence in the Nenetskij Avtonomnyj Okrug, Arctic Russia. Int J Circumpolar Health 2008; 67: 433-44.

335. Henson DE, Schwartz AM, Nsouli H, Albores-Saavedra J. Carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla of Vater share a field for carcinogenesis: a population-based study. Arch Pathol Lab Med 2009; 133: 67-71.

336. Toyoda Y, Nakayama T, Tsukuma H. Trends in home deaths among cancer death in Osaka, Japan-1995-2006. Gan To Kagaku Ryoho 2009; 36: 1131-4 (in Japanese).

337. Zhang J, Dhakal IB, Gross MD, Lang NP, Kadlubar FF, Harnack LJ, Anderson KE. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. Nutr Cancer 2009; 61: 457-65.

338. Zheng W, Lee SA. Well-done meat intake, heterocyclic amine exposure, and cancer risk. Nutr Cancer 2009; 61: 437-46.

339. Blackford A, Parmigiani G, Kensler TW, Wolfgang C, Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Eshleman JR, Goggins M, Jaffee EM, Iacobuzio-Donahue CA, Maitra A, Klein A, Cameron JL, Olino K, Schulick R, Winter J, Vogelstein B, Velculescu VE, Kinzler KW, Hruban RH. Genetic mutations associated with cigarette smoking in pancreatic cancer. Cancer Res 2009; 69: 3681-8.

340. La Torre G, de Waure C, Specchia ML, Nicolotti N, Capizzi S, Bilotta A, Clemente G, Ricciardi W. Does quality of observational studies affect the results of a meta-analysis?: The case of cigarette smoking and pancreatic cancer. Pancreas 2009; 38: 241-7.

341. Bersch VF, Osvaldt AB, Edelweiss MIA, Schumacher RA, Wendt LRR, Abreu LP, Blom CBB, Abreu GP, Costa L, Piccinini P, Rohde L. Effect of nicotine and cigarette smoke on an experimental model of intraepithelial lesions and pancreatic adenocarcinoma induced by 7,12-dimethylbenzanthracene in mice. Pancreas 2009; 38: 65-70.

342. Johansen D, Borgström A, Lindkvist B, Manjer J. Different markers of alcohol consumption, smoking and Body Mass Index in relation to risk of pancreatic cancer. A prospective cohort study within the Malmö Preventive Project. Pancreatology 2009; 9: 677-86.

343. Jiao L, Mitrou PN, Reedy J, Graubard BI, Hollenbeck AR, Schatzkin A, Stolzenberg-Solomon R. A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. Arch Intern Med 2009; 169: 764-70.

344. Jiao L, Flood A, Subar AF, Hollenbeck AR, Schatzkin A, Stolzenberg-Solomon R. Glycemic index, carbohydrates, glycemic load, and the risk of pancreatic cancer in a prospective cohort study. Cancer Epidemiol Biomarkers Prev 2009; 18: 1144-51.

345. Hui HX, Huang DS, McArthur D, Nissen N, Boros LG, Heaney AP. Direct spectrophotometric determination of serum fructose in pancreatic cancer patients. Pancreas 2009; 38: 706-12.

346. Bae JM, Lee EJ, Guyatt G. Citrus fruit intake and pancreatic cancer risk: a quantitative systematic review. Pancreas 2009; 38: 168-74.

347. Ianni E, Mignozzi K, Mitis F. Geographic epidemiologic descriptive study on the national priority site for remediation "Laguna di Grado e Marano." Eåidemiol Prev 2009; 33: 27-36 (in Italian).

348. Reddy N, Bhutani MS. Racial disparities in pancreatic cancer and radon exposure: a correlation study. Pancreas 2009; 38: 391-5.

349. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, Anderson KE, Hollis BW, Silverman DT. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. Cancer Res 2009; 69: 1439-47.

350. Stolzenberg-Solomon RZ, Sheffler-Collins S, Weinstein S, Garabrant DH, Mannisto S, Taylor P, Virtamo J, Albanes D. Vitamin E intake, alpha-tocopherol status, and pancreatic cancer in a cohort of male smokers. Am J Clin Nutr 2009; 89: 584-91.

351. Yang CY, Tsai SS, Chiu HF. Nitrate in drinking water and risk of death from pancreatic cancer in Taiwan. J Toxicol Environ Health A 2009; 72: 397-401.

352. Eriksen KT, Sørensen M, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, Raaschou-Nielsen O. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J Natl Cancer Inst 2009; 101: 605-9.

353. Ji J, Shu X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalised psoriasis patients: a follow-up study in Sweden. Br J Cancer 2009; 100: 1499-502.

354. Milne RL, Greenhalf W, Murta-Nascimento C, Real FX, Malats N. The inherited genetic component of sporadic pancreatic adenocarcinoma. Pancreatology 2009; 9: 206-14.

355. LaFemina J, Roberts PA, Hung YP, Gusella JF, Sahani D, Fernández-del Castillo C, Warshaw AL, Thayer SP. Identification of a novel kindred with familial pancreatitis and pancreatic cancer. Pancreatology 2009; 9: 273-9.

356. Greenhalf W, Grocock C, Harcus M, Neoptolemos J. Screening of high-risk families for pancreatic cancer. Pancreatology 2009; 9: 215-22.
357. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, Bandipalliam P, Stoffel EM, Gruber SB, Syngal S. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009; 302: 1790-5.

358. Koornstra JJ, Mourits MJ, Sijmons RH, Leliveld AM, Hollema H, Kleibeuker JH. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol 2009; 10: 400-8.

359. Buchholz M, Gress TM. Molecular changes in pancreatic cancer. Expert Rev Anticancer Ther 2009; 9: 1487-97.

360. Ranganathan P, Harsha HC, Pandey A. Molecular alterations in exocrine neoplasms of the pancreas. Arch Pathol Lab Med 2009; 133: 405-12.

361, Fujii K, Miyashita K, Yamada Y, Eguchi T, Taguchi K, Oda Y, Oda S, Yoshida MA, Tanaka M, Tsuneyoshi M. Simulation-based analyses reveal stable microsatellite sequences in human pancreatic cancer. Cancer Genet Cytogenet 2009; 189: 5-14.

362. Kahlert C, Weber H, Mogler C, Bergmann F, Schirmacher P, Kenngott HG, Matterne U, Mollberg N, Rahbari NN, Hinz U, Koch M, Aigner M, Weitz J. Increased expression of ALCAM/CD166 in pancreatic cancer is an independent prognostic marker for poor survival and early tumor relapse. Br J Cancer 2009; 101: 457-64.

363. Welsch T, Keleg S, Bergmann F, Bauer S, Hinz U, Schmidt J. Actinin-4 expression in primary and metastasized pancreatic ductal adenocarcinoma. Pancreas 2009; 38: 986-76.

364. Zhang C, Shao Y, Zhang W, Wu Q, Yang H, Zhong Q, Zhang J, Guan M, Yu B, Wan J. High-resolution melting analysis of ADAMTS9 methylation levels in gastric, colorectal, and pancreatic cancers. Ancer Genet Cytogenet 2010; 196: 38-44.

365. Bedrood S, Jayasinghe S, Sieburth D, Chen M, Erbel S, Butler PC, Langen R, Ritzel RA. Annexin A5 directly interacts with amyloidogenic proteins and reduces their toxicity. Biochemistry 2009; 48: 10568-76.

366. Ryschich E, Khamidjano A, Kerkadze V, Büchler MW, Zoller M, Schmidt J. Promotion of tumor cell migration by extracellular matrix proteins in human pancreatic cancer. Pancreas 2009; 38: 804-10.

367. Lawniczak M, Gawin A, Białek A, Lubiński J, Starzyńska T. Is there any relationship between BRCA1 gene mutation and pancreatic cancer development? Pol Arch Med Wewn 2008; 118: 645-9.

368. Yamato I, Sho M, Nomi T, Akahori T, Shimada K, Hotta K, Kanehiro H, Konishi N, Yagita H, Nakajima Y. Clinical importance of B7-H3 expression in human pancreatic cancer. Br J Cancer 2009; 101: 1709-16.

369. Seeley ES, Carrière C, Goetze T, Longnecker DS, Korc M. Pancreatic cancer and precursor pancreatic intraepithelial neoplasia lesions are devoid of primary cilia. Cancer Res 2009; 69: 422-30.

370. Zhao D, Xu D, Zhang X, Wang L, Tan W, Guo Y, Yu D, Li H, Zhao P, Lin D. Interaction of cyclooxygenase-2 variants and smoking in pancreatic cancer: a possible role of nucleophosmin. Gastroenterology 2009; 136: 1659-68.

371. Dewald GW, Smyrk TC, Thorland EC, McWilliams RR, Van Dyke DL, Keefe JG, Belongie KJ, Smoley SA, Knutson DL, Fink SR, Wiktor AE, Petersen GM. Fluorescence in situ hybridization to visualize genetic abnormalities in interphase cells of acinar cell carcinoma, ductal adenocarcinoma, and islet cell carcinoma of the pancreas. Mayo Clin Proc 2009; 84: 801-10.

372. Maréchal R, Demetter P, Nagy N, Berton A, Decaestecker C, Polus M, Closset J, Devière J, Salmon I, Van Laethem JL. High expression of CXCR4 may predict poor survival in resected pancreatic adenocarcinoma. Br J Cancer 2009; 100: 1444-51.

373. Scola L, Giacalone A, Marasà L, Mirabile M, Vaccarino L, Forte GI, Giannitrapani L, Caruso C, Montalto G, Lio D. Genetic determined downregulation of both type 1 and type 2 cytokine pathways might be protective against pancreatic cancer. Ann N Y Acad Sci 2009; 1155: 284-8.

374. Son K, Fujioka S, Iida T, Furukawa K, Fujita T, Yamada H, Chiao PJ, Yanaga K. Doxycycline induces apoptosis in PANC-1 pancreatic cancer cells. Anticancer Res 2009; 29: 3995-4003.

375. Laurent-Puig P, Lievre A, Blons H. Mutations and response to epidermal growth factor receptor inhibitors. Clin Cancer Res 2009; 15: 1133-9.

376. Cates JMM, Byrd RH, Fohn LE, Tatsas AD, Washington MK, Black CC. Epithelial-mesenchymal transition markers in pancreatic ductal adenocarcinoma. Pancreas 2009; 38: e1-6.

377. Guo QQ, Zhang B, Dong X, Xie QP, Guo EQ, Huang H, Wu Y. Elevated levels of plasma fibrinogen in patients with pancreatic cancer: possible role of a distant metastasis predictor. Pancreas 2009; 38: e75-9.

378. Gaisina IN, Gallier F, Ougolkov AV, Kim KH, Kurome T, Guo S, Holzle D, Luchini DN, Blond SY, Billadeau DD, Kozikowski AP. From a natural product lead to the identification of potent and selective benzofuran-3-yl-(indol-3-yl)maleimides as glycogen synthase kinase 3beta inhibitors that suppress proliferation and survival of pancreatic cancer cells. J Med Chem 2009; 52: 1853-63.

379. Hidalgo M, Maitra A. The hedgehog pathway and pancreatic cancer. N Eng J Med 2009; 361: 2094-6.

380. Liao WC, Wu MS, Wang HP, Tien YW, Lin JT. Serum heat shock protein 27 is increased in chronic pancreatitis and pancreatic carcinoma. Pancreas 2009; 38: 422-6.

381. Maréchal R, Van Laethem JL. HuR modulates gemcitabine efficacy: new perspectives in pancreatic cancer treatment. Expert Rev Anticancer Ther 2009; 9: 1439-41.

382. Hewish M, Chau I, Cunningham D. Insulin-like growth factor 1 receptor targeted therapeutics: novel compounds and novel treatment strategies for cancer medicine. Recent Pat Anticancer Drug Discov 2009; 4: 54-72.

383. Walsh N, Clynes M, Crown J, O'Donovan N. Alterations in integrin expression modulates invasion of pancreatic cancer cells. J Exp Clin Cancer Res 2009; 28: 140.

384. Fujisawa T, Joshi B, Nakajima A, Puri RK. A novel role of interleukin-13 receptor alpha2 in pancreatic cancer invasion and metastasis. Cancer Res 2009; 69: 8678-85.

385. Gidekel Friedlander SY, Chu GC, Snyder EL, Girnius N, Dibelius G, Crowley D, Vasile E, DePinho RA, Jacks T. Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras. Cancer Cell 2009; 16: 379-89.

386. Ji Z, Mei FC, Lory PL, Gilbertson SR, Chen Y, Cheng X. Chemical genetic screening of KRAS-based synthetic lethal inhibitors for pancreatic cancer. Front Biosci 2009; 14: 2904-10.

387. Uhland K, Siphos B, Arkona C, Schuster M, Petri B, Steinmetzer P, Mueller F, Schweinitz A, Steinmetzer T, Van De Locht A. Use of IHC and newly designed matriptase inhibitors to elucidate the role of matriptase in pancreatic ductal adenocarcinoma. Int J Oncol 2009; 35: 347-57.

388. Mizutani S, Miyato Y, Shidara Y, Asoh S, Tokunaga A, Tajiri T, Ohta S. Mutations in the mitochondrial genome confer resistance of cancer cells to anticancer drugs. Cancer Sci 2009 Jun 1 [Epub ahead of print].

389. Melisi D, Niu J, Chang Z, Xia Q, Peng B, Ishiyama S, Evans DB, Chiao PJ. Secreted interleukin-1alpha induces a metastatic phenotype in pancreatic cancer by sustaining a constitutive activation of nuclear factor-kappaB. Mol Cancer Res 2009; 7: 624-33.

390. Chipitsyna G, Gong Q, Anandanadesan R, Alnajar A, Batra SK, Wittel UA, Cullen DM, Akhter MP, Denhardt DT, Yeo CJ, Arafat HA. Induction of osteopontin expression by nicotine and cigarette smoke in the pancreas and pancreatic ductal adenocarcinoma cells. Int J Cancer 2009; 125: 276-85.

391. Chen JY, Amos CI, Merriman 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. Pancreatology 2009; 9: 1-4.

392. Taii A, Hamada S, Kataoka K, Yasukawa S, Sonoyama T, Okanoue T, Yanagisawa A. Correlations between p53 gene mutations and histologic characteristics of pancreatic ductal carcinoma. Pancreas 2009; 38: e60-7.

393. Ma J, Jiang Y, Jiang Y, Sun Y, Zhao X. Expression of nerve growth factor and tyrosine kinase receptor A and correlation with perineural invasion in pancreatic cancer. J Gastroenterol Hepatol 2008; 23: 1852-9.

394. Fesinmeyer MD, Stanford JL, Brentnall TA, Mandelson MT, Farin F, Srinouanprachanh S, Afsharinejad Z, Goodman GE, Barnett MJ, Austin MA. Association between the peroxisome proliferator-activated receptor-gamma Pro12Ala variant and haplotype and pancreatic cancer in a high-risk cohort of smokers: a pilot study. Pancreas 2009; 38: 631-7.

395. Hildenbrand R, Niedergethmann M, Marx A, Belharazem D, Allgayer H, Schleger C, Ströbel P. Amplification of the urokinase-type plasminogen activator receptor (uPAR) gene in ductal pancreatic carcinomas identifies a clinically high-risk group. Am J Pathol 2009; 174: 2246-53.

396. Eguchi H, Ishikawa O, Ohigashi H, Takahashi H, Yano M, Nishiyama K, Tomita Y, Uehara R, Takehara A, Nakamura Y, Nakagawa H. Serum REG4 level is a predictive biomarker for the response to preoperative chemoradiotherapy in patients with pancreatic cancer. Pancreas 2009; 38: 791-8.

397. Fernandes-Santos, Caroline MSc; Evangelista Carneiro R, de Souza Mendonca L, Barbosa Aguila M, Alberto Mandarim-de-Lacerda C. Rosiglitazone aggravates nonalcoholic fatty pancreatic disease in C57BL/6 mice fed high-fat and high-sucrose diet. Pancreas 2009; 38: e80-6.

398. Laklai H, Laval S, Dumartin L, Rochaix P, Hagedorn M, Bikfalvi A, Le Guellec S, Delisle MB, Schally AV, Susini C, Pyronnet S, Bousquet C. Thrombospondin-1 is a critical effector of oncosuppressive activity of sst2 somatostatin receptor on pancreatic cancer. Proc Natl Acad Sci USA 2009; 106: 17769-74.

399. Guillermet-Guibert J, Davenne L, Pchejetski D, Saint-Laurent N, Brizuela L, Guilbeau-Frugier C, Delisle MB, Cuvillier O, Susini C, Bousquet C. Targeting the sphingolipid metabolism to defeat pancreatic cancer cell resistance to the chemotherapeutic gemcitabine drug. Mol Cancer Ther 2009; 8: 809-20.

400. Hibi T, Mori T, Fukuma M, Yamazaki K, Hashiguchi A, Yamada T, Tanabe M, Aiura K, Kawakami T, Ogiwara A, Kosuge T, Kitajima M, Kitagawa Y, Sakamoto M. Synuclein-gamma is closely involved in perineural invasion and distant metastasis in mouse models and is a novel prognostic factor in pancreatic cancer. Clin Cancer Res 2009; 15: 2864-71.

401. Kubo T, Kuroda Y, Kokubu A, Hosoda F, Arai Y, Hiraoka N, Hirohashi S, Shibata T. Resequencing analysis of the human tyrosine kinase gene family in pancreatic cancer. Pancreas 2009; 38: e200-6.

402. Hildenbrand R, Niedergethmann M, Marx A, Belharazem D, Allgayer H, Schleger C, Ströbel P. Amplification of the urokinase-type plasminogen activator receptor (uPAR) gene in ductal pancreatic carcinomas identifies a clinically high-risk group. Am J Pathol 2009; 174: 2246-53.

403. Xue A, Xue M, Jackson C, Smith RC. Suppression of urokinase plasminogen activator receptor inhibits proliferation and migration of pancreatic adenocarcinoma cells via regulation of ERK/p38 signaling. Int J Biochem Cell Biol 2009; 41: 1731-8.

404. Neale RE, Youlden DR, Krnjacki L, Kimlin MG, van der Pols JC. Latitude variation in pancreatic cancer mortality in Australia. Pancreas 2009; 38: 387-90.

405. Tonack S, Aspinall-O'Dea M, Neoptolemos JP, Costello E. Pancreatic cancer: proteomic approaches to a challenging disease. Pancreatology 2009; 9: 567-76.

406. Cui Y, Wu J, Zong M, Song G, Jia Q, Jiang J, Han J. Proteomic profiling in pancreatic cancer with and without lymph node metastasis. Int J Cancer 2009; 124: 1614-21.

407. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. Arch Pathol Lab Med 2009; 133: 365-74.

408. Klein AP, Borges M, Griffith M, Brune K, Hong SM, Omura N, Hruban RH, Goggins M. Absence of deleterious palladin mutations in patients with familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2009; 18: 1328-30.

409. Shi C, Hong SM, Lim P, Kamiyama H, Khan M, Anders RA, Goggins M, Hruban RH, Eshleman JR. KRAS2 mutations in human pancreatic acinar-ductal metaplastic lesions are limited to those with PanIN: implications for the human pancreatic cancer cell of origin. Mol Cancer Res 2009; 7: 230-6.

410. Snyder CS, Kaushal S, Kono Y, Cao HS, Hoffman RM, Bouvet M. Complementarity of ultrasound and fluorescence imaging in an orthotopic mouse model of pancreatic cancer. BMC Cancer 2009; 9: 106.

411. Levy MJ, Gleeson FC, Zhang L. Endoscopic ultrasound fine-needle aspiration detection of extravascular migratory metastasis from a remotely located pancreatic cancer. Clin Gastroenterol Hepatol 2009; 7: 246-8.

412. Shibata K, Iwaki K, Kai S, Ohta M, Kitano S. Increased levels of both carbohydrate antigen 19-9 and Duke pancreatic monoclonal antigen type 2 reflect postoperative prognosis in patients with pancreatic carcinoma. Pancreas 2009; 38: 619-24.

413. Mayo SC, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG. Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? J Am Coll Surg 2009; 208: 87-95.

414. Yamada S, Nakao A, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Kodera Y, Takeda S. Pancreatic cancer with paraaortic lymph node metastasis: a contraindication for radical surgery? Pancreas 2009; 38: e13-7.

415. Klimstra DS, Pitman MB, Hruban RH. An algorithmic approach to the diagnosis of pancreatic neoplasms. Arch Pathol Lab Med 2009; 133: 454-64.

416. Mroczko B, Lukaszewicz-Zajac M, Wereszczynska-Siemiatkowska U, Groblewska M, Gryko M, Kedra B, Jurkowska G, Szmitkowski M. Clinical significance of the measurements of serum matrix metalloproteinase-9 and its inhibitor (tissue inhibitor of metalloproteinase-1) in patients with pancreatic cancer: metalloproteinase-9 as an independent prognostic factor. Pancreas 2009; 38: 613-8.

417. Faccioli N, Crippa S, Bassi C, D'Onofrio M. Contrast-enhanced ultrasonography of the pancreas. Pancreatology 2009; 9: 560-6.

418. Badea R, Seicean A, Diaconu B, Stan-Iuga R, Sparchez Z, Tantau M, Socaciu M. Contrast-enhanced ultrasound of the pancreas – a method beyond its potential or a new diagnostic standard? J Gastrointestin Liver Dis 2009; 18: 237-42.

419. Iglesias García J, Lariño Noia J, Domínguez Muñoz JE. Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer. Rev Esp Enferm Dig 2009; 101: 631-8.

420. Sreenarasimhaiah J. Interventional endoscopic ultrasound: the next frontier in gastrointestinal endoscopy. Am J Med Sci 2009: 338: 319-24.

421. Horwhat JD, Gerke H, Acosta RD, Pavey DA, Jowell PS. Focal or diffuse "fullness" of the pancreas on CT. Usually benign, but EUS plus/minus FNA is warranted to identify malignancy. JOP 2009; 10: 37-42.

422. Al-Haddad M, Khashab M, Zyromski N, Pungpapong S, Wallace MB, Scolapio J, Woodward T, Noh K, Raimondo M. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. Pancreas 2009; 38: 672-5.

423. Tadic C, Kujundzic M, Stoos-Veic T, Kaic G, Vukelic-Markovic M. Role of repeated endoscopic ultrasound-guided fine needle aspiration in small solid pancreatic masses with previous indeterminate and negative cytological finnings. Dig Dis 2008; 26: 377-82.

424. Krishna NB, LaBundy JL, Saripalli S, Safdar R, Agarwal B. Diagnostic value of EUS-FNA in patients suspected of having pancreatic cancer with a focal lesion on CT ccan/MRI but without obstructive jaundice. Pancreas 2009; 38: 625-30.

425. Eloubeidi MA, Tamhane A. Prospective assessment of diagnostic utility and complications of endoscopic ultrasound-guided fine needle aspiration. Results from a newly developed academic endoscopic ultrasound program. Dig Dis 2008; 26: 356-63.

426. Spier BJ, Johnson EA, Gopal DV, Frick T, Einstein MM, Byrne S, Koscik RL, Liou JI, Broxmeyer T, Selvaggi SM, Pfau PR. Predictors of malignancy and recommended follow-up in patients with negative endoscopic ultrasound-guided fine-needle aspiration of suspected pancreatic lesions. Can J Gastroenterol 2009; 23: 279-86.

427.Carrara S, Arcidiacono PG, Giussani A, Testoni PA. Acute hemorrhage with retroperitoneal hematoma after endoscopic ultrasound-guided fine-needle aspiration of an intraductal papillary mucinous neoplasm of the pancreas. Am J Gastroenterol 2009; 104: 1610-1.

428. Thomas T, Kaye PV, Ragunath K, Aithal G. Efficacy, safety, and predictive factors for a positive yield of EUS-guided Trucut biopsy: a large tertiary referral center experience. Am J Gastroenterol 2009; 104: 584-91.

429. Kawamoto S, Siegelman SS, Bluemke DA, Hruban RH, Fishman EK. Focal fatty infiltration in the head of the pancreas: evaluation with multidetector computed tomography with multiplanar reformation imaging. J Comput Assist Tomogr 2009; 33: 90-5.

430. Kawamoto S, Siegelman SS, Bluemke DA, Hruban RH, Fishman EK. Focal fatty infiltration in the head of the pancreas: evaluation with multidetector computed tomography with multiplanar reformation imaging. J Comput Aaist Tomogr 2009; 33: 90-5.

431. Jemaa Y, Houissa F, Trabelsi S, Moussa A, Belhouchet H, Mouelhi L, Bouraoui M, Bouzaidi S, Debbeche R, Ben Yedder J, Salem M, Najjar T. Endoscopic ultrasonography versus helical CT in diagnosis and staging of pancreatic cancer. Tunis Med 2008; 86: 346-9.

432. Rezai P, Mulcahy MF, Tochetto SM, Berggruen S, Yaghmai V. Morphological analysis of pancreatic adenocarcinoma on multidetector row computed tomography: implications for treatment response evaluation. Pancreatology 2009; 9: 799-803.

433. Klauss M, Alt CD, Welzel T, Werner J, Büchler MW, Richter GM, Kauffman n GW, Kauczor HU, Grenacher L. Multidetector CT evaluation of the course of nonresectable pancreatic carcinomas with neoadjuvant therapy. Pancreatology 2009; 9: 621-30.

434. Kim YE, Park MS, Hong HS, Kang CM, Choi JY, Lim JS, Lee WJ, Kim MJ, Kim KW. Effects of neoadjuvant combined chemotherapy and radiation therapy on the CT evaluation of resectability and staging in patients with pancreatic head cancer. Radiology 2009; 250: 758-65.

435. Park SS, Lee KT, Lee KH, Lee JK, Kim SH, Choi JY, Rhee JC. Diagnostic usefulness of PET/CT for pancreatic malignancy. Korean J Gastroenterol 2009; 54: 235-42 (in Korean).

436. Fattahi R, Balci NC, Perman WH, Hsueh EC, Alkaade S, Havlioglu N, Burton FR. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. J Magn Reson Imaging 2009; 29: 350-6.

437. Lauenstein TC, 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. Pancreatology 2009; 9: 71-5.

438. Kühn JP, Hegenscheid K, Siegmund W, Froehlich CP, Hosten N, Puls R. Normal dynamic MRI enhancement patterns of the upper abdominal organs: gadoxetic acid compared with gadobutrol. Am J Roentgenol 2009; 193: 1318-23.

439. Ueno M, Niwa T, Ohkawa S, Amano A. Masaki T, Miyakawa K, Yoshida T. The usefulness of perfusion-weighted magnetic resonance imaging in advanced pancreatic cancer. Pancreas 2009; 38: 644-8.

440. Feng M, Balter JM, Normolle D, Adusumilli S, Cao Y, Chenevert TL, Ben-Josef E. Characterization of pancreatic tumor motion using cine MRI: surrogates for tumor position should be used with caution. Int J Radiat Oncol Biol Phys 2009; 74: 884-91.

441. Yun EJ, Choi CS, Yoon DY, Seo YL, Chang SK, Kim JS, Woo JY. Combination of magnetic resonance cholangiopancreatography and computed tomography for preoperative diagnosis of the Mirizzi syndrome. J Comput Assist Tomogr 2009; 33: 636-40.

442. Uchida H, Hirooka Y, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ohmiya N, Niwa Y, Katano Y, Ishigami M, Goto H. Feasibility of tissue elastography using transcutaneous ultrasonography for the diagnosis of pancreatic diseases. Pancreatology 2009; 38: 17-22.

443. Giovannini M, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Geneviève M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol 2009; 15: 1587-93.

444. Zyromski NJ, Mathur A, Gowda GAN, Murphy C, Swartz-Basile DA, Wade TE, Pitt HA, Raftery D. Nuclear magnetic resonance spectroscopy-based metabolomics of the fatty pancreas: implicating fat in pancreatic pathology. Pancreatology 2009; 9: 410-9.

445. Turzhitsky V, Liu Y, Hasabou N, Goldberg M, Roy HK, Backman V, Brand R. Investigating population risk factors of pancreatic cancer by evaluation of optical markers in the duodenal mucosa. Dis Markers 2008; 25: 313-21.

446. Yong KT, Ding H, Roy I, Law WC, Bergey EJ, Maitra A, Prasad PN. Imaging pancreatic cancer using bioconjugated InP quantum dots. ACS Nano 2009; 3: 502-10.

447. Ko HW, Tsai YH, Yu CT, Huang CY, Chen CH. Good response to gefitinib for lung adenocarcinoma with hyperamylasemia: a case report. Chang Gung Med J 2008; 31: 606-11.

448. Ibis C, Albayrak D, Altan A. Primary hydatid disease of pancreas mimicking cystic neoplasm. South Med J 2009; 102: 529-30.

449. Akaraviputh T, Manuyakorn A, Lohsiriwat V. Diagnosis by endoscopic ultrasound of a large aberrant pancreas mimicking malignant gastrointestinal stromal tumor of the stomach. Endoscopy 2009; 41 Suppl 2: E63-4.

450. Klöppel G, Adsay NV. Chronic pancreatitis and the differential diagnosis versus pancreatic cancer. Arch Pathol Lab Med 2009; 133: 382-7.

451. Zamboni G, Capelli P, Scarpa A, Bogina G, Pesci A, Brunello E, Klöppel G. Nonneoplastic mimickers of pancreatic neoplasms. Arch Pathol Lab Med 2009; 133: 439-53.

452. Ashindoitiang JA, Anunobi CC, Atoyebi OA. Haemosuccus pancreaticus as a rare initial manifestation of pancreatic carcinoma. Nig Q Hosp Med 2008; 18: 191-3.

453. Wun T, White RH. Venous thromboembolism (VTE) in patients with cancer: epidemiology and risk factors. Cancer Invest 2009; 27 Suppl 1: 63-74.

454. Heidrich H, Konau E, Hesse P. Asymptomatic venous thrombosis in cancer patients – a problem often overlooked. Results of a retrospective and prospective study. Vasa 2009; 38: 160-6.

455. Kessler CM. The link between cancer and venous thromboembolism: a review. Am J Clin Oncol 2009; 32 (4 suppl): S3-7.

456. Davidson T, Goitein O, Avigdor A, Zwas ST, Goshen E. 18F-FDG-PET/CT for the diagnosis of tumor thrombosis. Isr Med Assoc J 2009; 11: 69-73.

457. Mathur A, Zyromski NJ, Pitt HA, Al-Azzawi H, Walker JJ, Saxena R, Lillemoe KD. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009; 208: 989-94.

458. Williams TK, Rosato EL, Kennedy EP, Chojnacki KA, Andrel J, Hyslop T, Doria C, Sauter PK, Bloom J, Yeo CJ, Berger AC. Impact of obesity on perioperative morbidity and mortality after pancreaticoduodenectomy. J Am Coll Surg 2009; 208: 210-7.

459. Fleming JB, Gonzalez RJ, Petzel MQ, Lin E, Morris JS, Gomez H, Lee JE, Crane CH, Pisters PW, Evans DB. Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. Arch Surg 2009; 144: 216-21.

460. Hong SG, Jung SJ, Joo MK, Lee BJ, Yeon JE, Park JJ, Byun KS, Bak YT. Prevalence of pancreatic cancer in diabetics and clinical characteristics of diabetes-associated with pancreatic cancer – comparison between diabetes with and without pancreatic cancer. Korean J Gastroenterol 2009; 54: 167-73 (in Korean).

461. Cecka F, Jon B, Havel E, Lojík M, Raupach J, Bělobrádek Z, Neoral C, Subrt Z, Ferko A. Truncus coeliacus stenosis in duodenopancreatectomy. Rozhl Chir 2009; 88: 192-5 (in Czech).

462. Coates JM, Beal SH, Russo JE, Vanderveen KA, Chen SL, Bold RJ, Canter RJ. Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. Arch Surg 2009; 144: 841-7.

463. Li ZJ, Zhang ZD, Hu WM, Zeng Y, Liu XB, Mai G, Zhang Y, Lu HM, Tian BL. Pancreaticoduodenectomy with preoperative obstructive jaundice: drainage or not. Pancreas 2009; 38: 379-86.

464. Yong KT. Mn-doped near-infrared quantum dots as multimodal targeted probes for pancreatic cancer imaging. Nanotechnology 2009; 20: 15102.

465. Papaxoinis K, Patsouris E, Athanassiadou P, Nicolopoulou-Stamati P. Contribution of nuclear morphometry by confocal laser scanning microscopy to the diagnosis of malignant bile duct strictures. Acta Cytol 2009; 53: 137-43.

466. Martignoni ME, Dimitriu C, Bachmann J, Krakowski-Rosen H, Ketterer K, Kinscherf R, Friess H. Liver macrophages contribute to pancreatic cancer-related cachexia. Oncol Rep 2009; 21: 363-9.

467. Legakis I, Stathopoulos J, Matzouridis T, Stathopoulos GP. Decreased plasma ghrelin levels in patients with advanced cancer and weight loss in comparison to healthy individuals. Anticancr Res 2009; 29: 3949-52.

468. Riall TS. What is the effect of age on pancreatic resection? Adv Surg 2009; 43: 233-49.

469. Pratt WB, Gangavati A, Agarwal K, Schreiber R, Lipsitz LA, Callery MP, Vollmer CM Jr. Establishing standards of quality for elderly patients undergoing pancreatic resection. Arch Surg 2009; 144: 950-6.

470. Fragulidis G, Arkadopoulos N, Vassiliou I, Marinis A, Theodosopoulos T, Stafyla V, Kyriazi M, Karapanos K, Dafnios N, Polydorou A, Voros D, Smyrniotis V. Pancreatic leakage after pancreaticoduodenectomy: the impact of the isolated jejunal loop length and anastomotic technique of the pancreatic stump. Pancreatology 2009; 9: e177-82.

471. Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, Hyslop T, Schmidt CM, Rosato EL, Lavu H, Nakeeb A, Pitt HA, Lillemoe KD, Yeo CJ. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 2009; 208: 738-47.

472. Fragulidis GP, Arkadopoulos N, Vassiliou I, Marinis A, Theodosopoulos T, Stafyla V, Kyriazi M, Karapanos K, Dafnios N, Polydorou A, Voros D, Smyrniotis V. Pancreatic leakage after pancreaticoduodenectomy: the impact of the isolated jejunal loop length and anastomotic technique of the pancreatic stump. Pancreas 2009; 38: e177-82.

473. You D, Jung K, Lee H, Heo J, Choi S, Choi D.. Comparison of different pancreatic anastomosis techniques using the definitions of the International Study Group of Pancreatic Surgery: a single surgeon's experience. Pancreas 2009; 38: 896-92.

474. Ozdemir A, Karakoc D, Hamaloglu E, Ozenc A. Pancreaticojejunostomy after pancreaticoduodenectomy: results of a new technique. Hepatogastroenterology 2009; 56: 285-9.

475. Tomimaru Y, Takeda Y, Kobayashi S, Marubashi S, Lee CM, Tanemura M, Nagano H, Kitagawa T, Dono K, Umeshita K, Wakasa K, Monden M. Comparison of postoperative morphological changes in remnant pancreas between pancreaticojejunostomy and pancreaticogastrostomy after pancreaticoduodenectomy. Pancreas 2009; 38: 203-7.

476. Yamamoto M, Hayashi MS, Nguyen NT, Nguyen TD, McCloud S, Imagawa DK. Use of Seamguard to prevent pancreatic leak following distal pancreatectomy. Arch Surg 2009; 144: 894-9.

477. Guzman EA, Nelson RA, Kim J, Pigazzi A, Trisal V, Paz B, Di Ellenhorn J. Increased incidence of pancreatic fistulas after the introduction of a bioabsorbable staple line reinforcement in distal pancreatic resections. Am Surg 2009; 75: 954-7.

478. Fujino Y, Matsumoto I, Ajiki T, Kuroda Y. Clinical reappraisal of total pancreatectomy for pancreatic disease. Hepatogastroenterology 2009; 56: 1525-8.

479. Harao M, Hishinuma S, Tomihawa M, Baba H, Ogata Y. Whole stomach and spleen preserving total pancreatectomy: a new surgical technique for pancreatic cancer. Hepatogastroenterology 2009; 56: 1549-51.

480. Martin RC 2nd, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg 2009; 144: 154-9.

481. Stauffer JA, Dougherty MK, Kim GP, Nguyen JH. Interposition graft with polytetrafluoroethylene for mesenteric and portal vein reconstruction after pancreaticoduodenectomy. Br J Surg 2009; 96: 247-52.

482. Braşoveanu V, Dumitraşcu T, Bacalbaşa N, Zamfir R. Splenic artery used for replaced common hepatic artery reconstruction during pancreatoduodenectomy – a case report. Chirurgia 2009; 104: 499-504.

483. Rosa F, Pacelli F, Papa V, Tortorelli AP, Bossola M, Doglietto GB. Iatrogenic lesion of the hepatic artery in the course of pancreatic surgery. Chir Ital 2009; 61: 485-92 (in Italian).

484. Sauvanet A. Lymph node resection for carcinoma of the pancreas. J Chir 2008; 145 Spc No 4: 12S31-5 (in French).

485. Chen XL, Ma Y, Wan Y, Duan LG. Experimental study of the safety of pancreas cryosurgery: the comparison of 2 different techniques of cryosurgery. Pancreatology 2009; 9: 92-6.

486. You DD, Jung KU, Lee HG, Heo JS, Choi SH, Choi DW. Comparison of different pancreatic anastomosis techniques using the definitions of the International Study Group of Pancreatic surgery: a single surgeon's experience. Pancreatology 2009; 9: 896-902.

487. Kato K, Yamada, Suguru S, Sugimoto H, Kanazumi N, Nomoto S, Takeda S, Kodera Y, Morita S, Nakao A. Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. Pancreas 2009; 38: 605-12.

488. Kelemen D, Papp R, Baracs J, Káposztás Z, Al-Farhat Y, Horváth OP. Treatment of pancreatic and periampullary tumours in our department in the last 10 years. Magy Seb 2009; 62: 287-92 (in Hungarian).

489. Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, Madura JA, Wiebke EA, Lillemoe KD. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006; 10: 1338-5.

490. Kuhlmann KF, de Castro SM, Wesseling JG, ten Kate FJ, Offerhaus GJ, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients. Eur J Cancer 2004; 40: 549-58.

491. Adham M, Jaeck D, Le Borgne J, Oussoultzouglou E, Chenard-Neu MP, Mosnier JF, Scoazec JY, Mornex F, Partensky C. Long-term survival (5-20 years) after pancreatectomy for pancreatic ductal adenocarcinoma: a series of 30 patients collected from 3 institutions. Pancreas 2008; 37: 352-7.
492. Conlon KC, Klimstra DS, Brennan MF. Long term survival after curative resection for pancreatic ductal adenocarcinoma. Ann Surg 1996; 223: 273-9.

493. Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003: 27:3 24-9.

494. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, Strasberg S, Hanna S, Taylor B, Langer B, Gallinger S. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg 2004; 198: 722-31.

495. Takai S, Satoi S, Toyokawa H, Yanagimoto H, Sugimoto N, Tsuji K, Araki H, Matsui Y, Imamura A, Kwon AH, Kamiyama Y. Clinicopathologic evaluation after resection for ductal adenocarcinoma of the pancreas: a retrospective, single institution experience. Pancreas 2003; 236: 243-9.

496. Kure S, Kaneko T, Takeda S, Inoue S, Nakao A. Analysis of long-term survivors after surgical resection of invasive pancreatic cancer. HPB 2005; 7: 129-34.

497. Han SS, Jang JY, Kim SW, Kim WH, Lee KU, Park YH. Analysis of long-term survivors after resection for pancreatic cancer. Pancreas. 2006; 32: 271-5.

498. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, Gullerud RE, Donohue JH, Nagorney DM, Farnell MB. Long term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg 2008; 247: 456-62.

499. Gudjonsson B. Carcinoma of the pancreas: critical analysis of costs, results of resections, and the need for standardized reporting. J Am Coll Surg 1995; 181: 483-503.

500. Bradley EL. Pancreatectomy for pancreatic adenocarcinoma: triumph, triumphalism, or transition. Arch Surg 2002; 137: 771-3.

501. Trede M, Schwall G, Saeger H-D. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990; 211: 447-58.

502. Riall TS, Cameron JL, Lillemoe KD, Winter JM, Campbell KA, Hruban RH, Chang D, Yeo CJ. Resected periampullary adenocarcinoma: 5-year survivors and their 6 to 10 year follow-up. Surgery. 2006; 140: 764-72.

503. Hernandez LV, Bhutani MS, Eisner M, Guda NM, Lu Na, Geenen JE, Catalano MF. Non-surgical tissue biopsy among patients with advanced pancreatic cancer: effect on survival. Pancreas 2009; 38: 289-92.

504. Pezzolla A, Lattarulo S, De Luca GM, Borrello G, Fucilli F, Marano G, Fabiano G, Palasciano N. Management of intrahepatic biliary lithiasis after pancreatic cancer surgery. Chir Ital 2008; 60: 843-8.

505. 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. Pancreatology 2009; 9: e48-54.

506. Nathan H, Cameron JL, Goodwin CR, Seth AK, Edil BH, Wolfgang CL, Pawlik TM, Schulick RD, Choti MA. Risk factors for pancreatic leak after distal pancreatectomy. Ann Surg 2009; 250: 277-81.
507. Lee SE, Jang JY, Lee KU, Kim SW. Clinical comparison of distal pancreatectomy with or without splenectomy. J Korean Med Sci 2008; 23: 1011-4.

508. Nakeeb A. Laparoscopic pancreatic resections. Adv Surg 2009; 43: 91-102.

509. Merchant NB, Parikh AA, Kooby DA. Should all distal pancreatectomies be performed laparoscopically? Adv Surg 2009; 43: 283-300.

510. Baker MS, Bentrem DJ, Ujiki MB, Stocker S, Talamonti MS. A prospective single institution comparison of peri-operative outcomes for laparoscopic and open distal pancreatectomy. Surgery 2009; 146: 635-43.

511. Das De S, Kow AW, Liau KH, Lim KH, Ho CK. Novel approach to laparoscopic resection of tumours of the distal pancreas. ANZ J Surg 2009; 79: 288-93.

512. Willingham FF, Gee DW, Sylla P, Kambadakone A, Singh AH, Sahani D, Mino-Kenudson M, Rattner DW, Brugge WR. Natural orifice versus conventional laparoscopic distal pancreatectomy in a porcine model: a randomized, controlled trial. Gastrointest Endosc 2009:70: 740-7.

513. Iwasaki Y, Sawada T, Kijima H, Kosuge T, Katoh M, Rokkaku K, Kita J, Shimoda M, Kubota K. Estimated glomerular filtration rate is superior to measured creatinine clearance for predicting postoperative renal dysfunction in patients undergoing pancreatoduodenectomy. Pancreatology 2009; 9: 20-5.

514. Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, Maeda H, Yatabe T, Kohsaki T, Kobayashi M, Hanazaki K. Continuous postoperative blood glucose monitoring and control by artificial pancreas in patients having pancreatic resection: a prospective randomized clinical trial. Arch Surg 2009; 144: 933-7.

515. Ohtsuka T, Kitahara K, Kohya N, Miyoshi A, Miyazaki K. Improvement of glucose metabolism after a pancreatoduodenectomy. Pancreas 2009; 38: 700-5.

516. Locher JL, Robinson CO, Bailey FA, Carroll WR, Heimburger DC, Magnuson JS, Saif MW, Ritchie CS. The contribution of social factors to undereating in older adults with cancer. J Support Oncol 2009; 7: 168-73.

517. Isayama H, Nakai Y, Togawa O, Kogure H, Ito Y, Sasaki T, Sasahira N, Hirano K, Tsujino T, Tada M, Kawabe T, Omata M. Covered metallic stents in the management of malignant and benign pancreatobiliary strictures. J Hepatobiliary Pancreat Surg 2009; 16: 624-7.

518. Weber A, Mittermeyer T, Wagenpfeil S, Schmid R, Prinz C. Self-expanding metal stents versus polyethylene stents for palliative treatment in patients with advanced pancreatic cancer. Pancreas 2009; 38: e7-12.

519. de Castro SM, Biere SS, Lagarde SM, Busch OR, van Gulik TM, Gouma DJ. Validation of a nomogram for predicting survival after resection for adenocarcinoma of the pancreas. Br J Surg 2009; 96: 417-23.

520. Stocken DD, Hassan AB, Altman DG, Billingham LJ, Bramhall SR, Johnson PJ, Freemantle N. Modelling prognostic factors in advanced pancreatic cancer. Br J Cancer 2008; 99: 883-93.

521. Kostro J, Sledziński Z. Quality of life after surgical treatment of pancreatic cancer. Acta Chir Belg 2008; 108: 679-84.

522. Bilimoria KY, Bentrem DJ, Lillemoe KD, Talamonti MS, Ko CY, Allen PJ, Aranha GV, Bentrem DJ, Evans DB, Lillemoe KD, Pisters PW, Schulick RD, Sener SF, Talamonti MS, Vickers SM, Warshaw AL, Yeo CJ, Kelsen DP, Picozzi VJ, Tempero MA, Abrams RA, Willett CG, Adsay NV, Megibow AJ, Sherman S. Assessment of pancreatic cancer care in the United States based on formally developed quality indicators. J Natl Cancer Inst 2009; 101: 848-59.

523. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. CA Cancer J Clin 2009; 59: 192-211.

524. Mackenzie RP, McCollum AD. Novel agents for the treatment of adenocarcinoma of the pancreas. Expert Rev Anticancer Ther 2009; 9: 1473-85.

525. Wilkowski R, Boeck S, Ostermaier S, Sauer R, Herbst M, Fietkau R, Flentje M, Miethe S, Boettcher HD, Scholten T, Bruns CJ, Rau HG, Hinke A, Heinemann V. Chemoradiotherapy with concurrent gemcitabine and cisplatin with or without sequential chemotherapy with gemcitabine/cisplatin vs chemoradiotherapy with concurrent 5-fluorouracil in patients with locally advanced pancreatic cancer – a multi-centre randomised phase II study. Br J Cancer 2009; 101: 1853-9.

526. Satoi S, Yanagimoto H, Toyokawa H, Takahashi K, Matsui Y, Kitade H, Mergental H, Tanigawa N, Takai S, Kwon AH. Surgical results after preoperative chemoradiation therapy for patients with pancreatic cancer. Pancreas 2009; 38: 282-8.

527. Merchant NB, Rymer J, Koehler EA, Ayers GD, Castellanos J, Kooby DA, Weber SH, Cho CS, Schmidt CM, Nakeeb A, Matos JM, Scoggins CR, Martin RC, Kim HJ, Ahmad SA, Chu CK, McClaine R, Bednarski BK, Staley CA, Sharp K, Parikh AA. Adjuvant chemoradiation therapy for pancreatic adenocarcinoma: who really benefits? J Am Coll Surg 2009; 208: 829-38.

528. Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, Yano M, Nakaizumi A, Uehara H, Tomita Y, Nishiyama K. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 2009; 250: 88-95.

529. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Büchler MW. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer 2009; 100: 246-50.

530. Kurosaki I, Kawachi Y, Nihei K, Tsuchiya Y, Aono T, Yokoyama N, Shimizu T, Hatakeyama K. Liver perfusion chemotherapy with 5-fluorouracil followed by systemic gemcitabine administration for resected pancreatic cancer: Preliminary results of a prospective phase 2 study. Pancreas 2009; 38: 161-7.

531. Turrini O, Viret F, Moureau-Zabotto L, Guiramand J, Moutardier V, Lelong B, de Chaisemartin C, Giovannini M, Delpero JR. Neoadjuvant 5-fluorouracil-cisplatin chemoradiation effect on survival in patients with resectable pancreatic head adenocarcinoma: a ten-year single institution experience. Oncology 2009; 76: 413-9.

532. Moody JS, Sawrie SM, Kozak KR, Plastaras JP, Howard G, Bonner JA. Adjuvant radiotherapy for pancreatic cancer is associated with a survival benefit primarily in stage IIB patients. J Gastroenterol 2009; 44: 84-91.

533. Davila JA, Chiao EY, Hasche JC, Petersen NJ, McGlynn KA, Shaib YH. Utilization and determinants of adjuvant therapy among older patients who receive curative surgery for pancreatic cancer. Pancreas 2009; 38: e18-25.

534. Tawada K, Yamaguchi T, Kobayashi A, Ishihara T, Sudo K, Nakamura K, Hara T, Denda T, Matsuyama M, Yokosuka O. Changes in tumor vascularity depicted by contrast-enhanced ultrasonography as a predictor of chemotherapeutic effect in patients with unresectable pancreatic cancer. Pancreas 2009; 38: 30-5.

535. Tsumura T, Matsuo H, Maruo T, Kawakami H, Hatano K, Saito S, Nishijima N, Nakatsuji M, Ikeda A, Nishikawa H, Kita R, Okabe Y, Kimura T, Amitani R, Osaki Y. Seven cases of gemcitabine-induced lung injury during treatment for pancreatic or biliary tract cancers. Gan To Kagaku Ryoho 2009; 36: 785-8 (in Japanese).

536. Ishibashi Y, Ito Y. A case of drug induced interstitial pneumonitis after gemcitabine treatment for pancreatic carcinoma. Gan To Kagaku Ryoho 2009; 36: 651-3 (in Japanese).

537. Recchia F, Sica G, Candeloro G, Bisegna R, Bratta M, Bonfili P, Necozione S, Tombolini V, Rea S. Chemoradioimmunotherapy in locally advanced pancreatic and biliary tree adenocarcinoma: a multicenter phase II study. Pancreas 2009; 38: e163-8.

538. Fukada I, Ikeda H, Yamaguchi K, Okabe M, Tsuruta A, Morimoto Y, Kawamoto K, Sano K, Paku T, Imai S, Yoshida Y, Ito T, Ogasahara K. A case of recurrent pancreatic cancer with lung metastasis responding to S-1 combined gemcitabine chemotherapy. Gan To Kagaku Ryoho 2009; 36: 1733-6 (in Japanese).

539. Sasajima J, Tanno S, Koizumi K, Nakano Y, Habiro A, Chiba A, Fujii T, Sugiyama Y, Nakamura K, Nishikawa T, Mizukami Y, Okumura T, Kohgo Y. Gemcitabine in combination with S-1 or UFT in patients with advanced pancreatic cancer Gan To Kagaku Ryoho 2009; 36: 1657-61 (in Japanese).

540. Neri B, Cipriani G, Grifoni R, Molinara E, Pantaleo P, Rangan S, Vannini A, Tonelli P, Valeri A, Pantalone D, Taddei A, Bechi P. Gemcitabine plus irinotecan as first-line weekly therapy in locally advanced and/or metastatic pancreatic cancer. Oncol Res 2009; 17: 559-64.

541. Galloway NR, Aspe JR, Sellers C, Wall NR. Enhanced antitumor effect of combined gemcitabine and proton radiation in the treatment of pancreatic cancer. Pancreatology 2009; 9: 782-90.

542. Graeser R, Bornmann C, Esser N, Ziroli V, Jantscheff P, Unger C, Hopt UT, Schaechtele C, von Dobschuetz E, Massing U. Antimetastatic effects of liposomal gemcitabine and empty liposomes in an orthotopic mouse model of pancreatic cancer. Pancreas 2009; 38: 330-7.

543. Niki T, Soejima T, Yoshikawa T, Yamamoto Y, Fujii O, Ohta Y, Tsuda M, Horita K, Tsujino K, Hirohata S, Fujino Y, Nishisaki H. 5-FU based chemoradiotherapy for unresectable locally advanced pancreatic cancer. Gan To Kagaku Ryoho 2009; 36: 63-9 (in Japanese).

544. Novarino A, Satolli MA, Chiappino I, Giacobino A, Bellone G, Rahimi F, Milanesi E, Bertetto O, Ciuffreda L. Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. Am J Clin Oncol 2009; 32: 44-8.

545. Pino MS, Milella M, Gelibter A, Sperduti I, De Marco S, Nuzzo C, Bria E, Carpanese L, Ruggeri EM, Carlini P, Cognetti F. Capecitabine and celecoxib as second-line treatment of advanced pancreatic and biliary tract cancers. Oncology 2009; 76: 254-61.

546. Niki T, Yamamoto Y, Tsuda M, Horita K, Hirohata S, Nishisaki H. Retrospective analysis of uracil/tegafur, cyclophosphamide and gemcitabine compared with gemcitabine monotherapy in unresectable pancreatic cancer. Gan To Kagaku Ryoho 2009; 36: 273-8 (in Japanese).

547. Sugimoto K, Okada K, Nakahira S, Okamura S, Miki H, Nakata K, Suzuki R, Yoshimura M, Uji K, Yoshida A, Tamura S. A case of metastatic pancreatic cancer after combination chemotherapy with uracil-tegafur and gemcitabine. Gan To Kagaku Ryoho 2009; 36: 321-3.

548. Yoo C, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, Lee SS, Seo DW, Lee SK, Kim MH, Han DJ, Kim SC, Lee JL. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer 2009; 101: 1658-63.

549. Carvajal RD, Tse A, Shah MA, Lefkowitz RA, Gonen M, Gilman-Rosen L, Kortmansky J, Kelsen DP, Schwartz GK, O'Reilly EM. A phase II study of flavopiridol (Alvocidib) in combination with docetaxel in refractory, metastatic pancreatic cancer. Pancreatology 2009; 9: 404-9.

550. Okamoto N, Inaba K, Konno H. Continuous treatment with S-1, an effective strategy for an older adult with unresectable advanced pancreatic cancer with peritoneal dissemination – a case report. Gan To Kagaku Ryoho 2009; 36: 1187-9 (in Japanese).

551. Brell JM, Matin K, Evans T, Volkin RL, Kiefer GJ, Schlesselman JJ, Dranko S, Rath L, Schmotzer A, Lenzner D, Ramanathan RK. Phase II study of docetaxel and gefitinib as second-line therapy in gemcitabine pretreated patients with advanced pancreatic cancer. Oncology 2009; 76: 270-4.

552. Maemura K, Shinchi H, Noma H, Mataki Y, Kurahara H, Maeda S, Natsugoe S, Takao S. Chemoradiotherapy for locally recurrence after primary resection of biliary-pancreatic cancer. Gan To Kagaku Ryoho 2009; 36: 265-8 (in Japanese).

553. Hirooka Y, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ishikawa T, Matsubara H, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Yamamoto K, Kaneko T, Nieda M, Yokokawa K, Goto H. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. Pancreas 2009; 38: e69-74.

554. Black JW. Reflections on some pilot trials of gastrin receptor blockade in pancreatic cancer. Eur J Cancer 2009; 45: 360-4.

555. Karacay H, Sharkey RM, Gold DV, Ragland DR, McBride WJ, Rossi EA, Chang CH, Goldenberg DM. Pretargeted radioimmunotherapy of pancreatic cancer xenografts: TF10-90Y-IMP-288 alone and combined with gemcitabine. J Nucl Med 2009; 50: 2008-16.

556. Eguchi H, Ishikawa O, Ohigashi H, Takahashi H, Yano M, Nishiyama K, Tomita Y, Uehara R, Takehara A, Nakamura Y, Nakagawa H. Serum REG4 level is a predictive biomarker for the response to preoperative chemoradiotherapy in patients with pancreatic cancer. Pancreatology 2009; 9: 791-8.

557. Zhang D, Ma QY, Shen SG, Hu HT. Inhibition of pancreatic cancer cell proliferation by propranolol occurs through apoptosis induction: the study of beta-adrenoceptor antagonist's anticancer effect in pancreatic cancer cell. Pancreas 2009; 38: 94-10.

558. Ohguri T, Imada H, Yahara K, Narisada H, Morioka T, Nakano K, Korogi Y. Concurrent chemoradiotherapy with gemcitabine plus regional hyperthermia for locally advanced pancreatic carcinoma: initial experience. Radiat Med 2008; 26: 587-96.

559. Miller RC, Iott MJ, Corsini MM. Review of adjuvant radiochemotherapy for resected pancreatic cancer and results from Mayo Clinic for the 5th JUCTS symposium. Int J Radiat Oncol Biol Phys 2009; 75: 364-8.

560. Maemura K, Shinchi H, Noma H, Mataki Y, Kurahara H, Maeda S, Natsugoe S, Takao S. Chemoradiotherapy for locally recurrence after primary resection of biliary-pancreatic cancer. Gan To Kagaku Ryoho 2009; 36: 265-8 (in Japanese).

561. Tawada K, Yamaguchi T, Kobayashi A, Ishihara T, Sudo K, Nakamura K, Hara T, Denda T, Matsuyama M, Yokosuka O. Changes in tumor vascularity depicted by contrast-enhanced ultrasonography as a predictor of chemotherapeutic effect in patients with unresectable pancreatic cancer. Pancreas 2009; 38: 30-5.

562. Kumagai M, Hara R, Mori S, Yanagi T, Asakura H, Kishimoto R, Kato H, Yamada S, Kandatsu S, Kamada T. Impact of intrafractional bowel gas movement on carbon ion beam dose distribution in pancreatic radiotherapy. Int J Radiat Oncol Biol Phys 2009; 73: 1276-81.

563. Spry N, Bydder S, Harvey J, Borg M, Ngan S, Millar J, Graham P, Zissiadis Y, Kneebone A, Ebert M. Accrediting radiation technique in a multicentre trial of chemoradiation for pancreatic cancer. J Med Imaging Radiat Oncol 2008; 52: 598-604.

564. Mackenzie RP, McCollum AD. Novel agents for the treatment of adenocarcinoma of the pancreas. Expert Rev Anticancer Ther 2009; 9: 1473-85.

565. Abe Y, Ito T, Baba E, Nagafuji K, Kawabe K, Choi I, Arita Y, Miyamoto T, Teshima T, Nakano S, Harada M. Nonmyeloablative allogeneic hematopoietic stem cell transplantation as immunotherapy for pancreatic cancer. Pancreas 2009; 38: 815-9.

566. Drag M, Surowiak P, Drag-Zalesinska M, Dietel M, Lage H, Oleksyszyn J. Comparision of the cytotoxic effects of birch bark extract, betulin and betulinic acid towards human gastric carcinoma and pancreatic carcinoma drug-sensitive and drug-resistant cell lines. Molecules 2009; 14: 1639-51.

567. Sahu RP, Batra S, Srivastava SK. Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. Br J Cancer 2009; 100: 1425-33.

568. Lissoni P, Rovelli F, Brivio F, Zago R, Colciago M, Messina G, Mora A, Porro G. A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus Aloe arborescens in patients with metastatic cancer. In vivo 2009; 23: 171-5.

569. Joo KR, Shin HP, Cha JM, Nam S, Huh Y. Effect of Korean red ginseng on superoxide dismutase inhibitor-induced pancreatitis in rats: a histopathologic and immunohistochemical study. Pancreas 2009; 38: 661-6.

570. Khashab MA, Emerson RE, DeWitt JM. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of anaplastic pancreatic carcinoma: a single-center experience. Pancreatology 2009; 9: 88-91.

571. Bauer A, Kleeff J, Bier M, Wirtz M, Kayed H, Esposito I, Korc M, Hafner M, Hoheisel JH, Friess H. Identification of malignancy factors by analyzing cystic tumors of the pancreas Pancreatology 2009; 9: 34-44.

572. Buscaglia JM, Giday SA, Kantsevoy SV, Jagannath SB, Magno P, Wolfgang CL, Daniels JA, Canto MI, Okolo PI. Patient- and cyst-related factors for improved prediction of malignancy within cystic lesions of the pancreas. Pancreatology 2009; 9: 631-8.

573. Leffler J, Krejcí T. Cystic neoplasms of the pancreas. Rozhl Chir 2008; 87: 456-8 (in Czech).

574. Basturk O, Coban I, Adsay NV. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. Arch Pathol Lab Med 2009; 133: 423-38.

575. Khalid A, Funch-Jensen P, Bendix J, Dutoit Hamilton S, Kruse A, Viborg Mortensen F. Intraductal papillary mucinous tumor of the pancreas (IPMT): follow-up of twelve cases. Scand J Surg 2009; 98: 25-9.

576. Tanno S, Sasajima J, Koizumi K, Yanagawa N, Nakano Y, Osanai M, Mizukami Y, Fujii T, Obara T, Okumura T, Kohgo Y. Tumor doubling time in two cases of main duct intraductal papillary-mucinous neoplasms of the pancreas. Hepatogastroenterology 2009; 56: 1545-8.

577. Ferrone CR, Correa-Gallego C, Warshaw AL, Brugge WR, Forcione DG, Thayer SP, Fernández-del Castillo C. Current trends in pancreatic cystic neoplasms. Arch Surg 2009; 144: 448-54.

578. Sahani DV, Lin DJ, Venkatesan AM, Sainani N, Mino-Kenudson M, Brugge WR, Fernandez-Del-Castillo C. Multidisciplinary approach to diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas. Clin Gastroenterol Hepatol 2009; 7: 259-69.

579. Tanno S, Nakano 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. Pancreatology 2009; 9: 36-40.

580. Fritz S, Fernandez-del Castillo C, Mino-Kenudson M, Crippa S, Deshpande V, Lauwers GY, Warshaw AL, Thayer SP, Iafrate AJ. Global genomic analysis of intraductal papillary mucinous neoplasms of the pancreas reveals significant molecular differences compared to ductal adenocarcinoma. Ann Surg 2009; 249: 440-7.

581. Koizumi K, Fujii T, Matsumoto A, Sugiyama R, Suzuki S, Sukegawa R, Ozawa K, Orii F, Taruishi M, Saitoh Y, Sotokawa M, Takada A. Synchronous double invasive ductal carcinomas of the pancreas with multifocal branch duct intraductal papillary mucinous neoplasms of the pancreas. Nippon Shokakibyo Gakkai Zasshi 2009; 106: 98-105 (in Japanese).

582. Woo SM, Ryu JK, Lee SH, Yoon WJ, Kim YT, Yoon YB. Branch duct intraductal papillary mucinous neoplasms in a retrospective series of 190 patients. Br J Surg 2009; 96: 405-11.

583. Satoi S, Takeyama Y, Nakai T, Haji S, Yasuda C, Ishikawa H, Yasuda T, Shinzaki W, Kamei K, Ohyanagi H. Diameter of main pancreatic duct is important for prediction of malignancy of IPMN. Pancreas 2009; 38: Sep 2 [Epub ahead of print].

584. Nara S, Onaya H, Hiraoka N, Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T. Preoperative evaluation of invasive and noninvasive intraductal papillary-mucinous neoplasms of the pancreas: clinical, radiological, and pathological analysis of 123 cases. Pancreas 2009; 38: 8-16.

585. 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. Pancreatology 2009; 9: 31-5.

586. Shimizu K, Itoh T, Shimizu M, Ku Y, Hori Y. CD133 expression pattern distinguishes intraductal papillary mucinous neoplasms from ductal adenocarcinomas of the pancreas. Pancreatology 2009; 9: e207-14.

587. Toll AD, Witkiewicz AK, Bibbo M. Expression of K homology domain containing protein (KOC) in pancreatic cytology with corresponding histology. Acta Cytol 2009; 53: 123-9.

588. Nakayama S, Semba S, Maeda N, Matsushita M, Kuroda Y, Yokozaki H. Hypermethylation-mediated reduction of WWOX expression in intraductal papillary mucinous neoplasms of the pancreas. Br J Cancer 2009; 100: 1438-43.

589. Nakagawa A, Yamaguchi T, Ohtsuka M, Ishihara T, Sudo K, Nakamura K, Hara T, Denda T, Miyazaki M. Usefulness of multidetector computed tomography for detecting protruding lesions in intraductal papillary mucinous neoplasm of the pancreas in comparison with single-detector computed tomography and endoscopic ultrasonography. Pancreas 2009; 38: 131-36.

590. Hirano S, Kondo S, Tanaka E, Shichinohe T, Suzuki O, Shimizu M, Itoh T. Role of CT in detecting malignancy during follow-up of patients with branch-type IPMN of the pancreas.

Hepatogastroenterology 2009; 56: 515-8.

591. Yoon LS, Catalano OA, Fritz S, Ferrone CR, Hahn PF, Sahani DV. Another dimension in magnetic resonance cholangiopancreatography: comparison of 2- and 3-dimensional magnetic resonance cholangiopancreatography for the evaluation of intraductal papillary mucinous neoplasm of the pancreas. J Comput Assist Tomogr 2009; 33: 363-8.

592. Ringold DA, Shroff P, Sikka SK, Ylagan L, Jonnalagadda S, Early DS, Edmundowicz SA, Azar R. Pancreatitis is frequent among patients with side-branch intraductal papillary mucinous neoplasia diagnosed by EUS. Gastrointest Endosc 2009 Jun 23 [Epub ahead of print].

593. Pala C, Serventi F, Scognamillo F, Attene F, Pisano IP, Cugia L, Meloni M, Trignano M. Cystic pancreatic tumor treated by distal spleno-pancreatectomy with occasional diagnosis of neuroendocrine tumor: case report. Ann Ital Chir 2008; 79: 451-6 (in Italian).

594. Oh SJ, Lee SJ, Lee HY, Paik YH, Lee DK, Lee KS, Chung JB, Yu JS, Yoon DS. Extrapancreatic tumors in intraductal papillary mucinous neoplasm of the pancreas. Korean J Gastroenterol 2009; 54: 162-6 (in Korean).

595. Hirono S, Tani M, Kawai M, Ina S, Nishioka R, Miyazawa M, Fujita Y, Uchiyama K, Yamaue H. Treatment strategy for intraductal papillary mucinous neoplasm of the pancreas based on malignant predictive factors. Arch Surg 2009; 144: 345-9.

596. Gill KR, Pelaez-Luna M, Keaveny A, Woodward TA, Wallace MB, Chari ST, Smyrk TC, Takahashi N, Clain JE, Levy MJ, Pearson RK, Petersen BT, Topazian MD, Vege SS, Kendrick M, Farnell MB, Raimondo M. Branch duct intraductal papillary mucinous neoplasm of the pancreas in solid organ transplant recipients. Am J Gastroenterol 2009; 104: 1256-61.

597. Nara S, Shimada K, Sakamoto Y, Esaki M, Kosuge T, Hiraoka N. Clinical significance of frozen section analysis during resection of intraductal papillary mucinous neoplasm: should a positive pancreatic margin for adenoma or borderline lesion be resected additionally? J Am Coll Surg 2009; 209: 614-21.

598. Ishikawa T, Takeda K, Itoh M, Imaizumi T, Oguri K, Takahashi H, Kasuga H, Toriyama T, Matsuo S, Hirooka Y, Itoh A, Kawashima H, Kasugai T, Ohno E, Miyahara R, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Goto H. Prevalence of pancreatic cystic lesions including intraductal papillary mucinous neoplasms in patients with end-stage renal disease on hemodialysis. Pancreas 2009; 38: 175-9.

599. Wargo JA, Fernandez-del-Castillo C, Warshaw AL. Management of pancreatic serous cystadenomas. Adv Surg 2009; 43: 23-34.

600. Allen PJ, Qin LX, Tang L, Klimstra D, Brennan MF, Lokshin A. Pancreatic cyst fluid protein expression profiling for discriminating between serous cystadenoma and intraductal papillary mucinous neoplasm. Ann Surg 2009; 250: 754-60.

601. Agarwal N, Kumar S, Dass J, Arora VK, Rathi V. Diffuse pancreatic serous cystadenoma associated with neuroendocrine carcinoma: a case report and review of literature. JOP 2009; 10: 55-8.

602. Marsh WL, Colonna J, Yearsley M, Bloomston M, Frankel WL. Calponin is expressed in serous cystadenomas of the pancreas but not in adenocarcinomas or endocrine tumors. Appl Immunohistochem Mol Morphol 2009; 17: 216-9.

603. Akiyama T, Sadahira Y, Irei I, Nishimura H, Hida AI, Notohara K, Hamazaki S. Pancreatic serous microcystic adenoma with extensive oncocytic change. Pathol Int 2009; 59: 102-6.

604. Hisa T, Ohkubo H, Shiozawa S, Ishigame H, Ueda M, Takamatsu M, Furutake M. Mucinous cystadenoma of the pancreas with huge mural hematoma. Pathol Int 2009; 59: 762-5.

605. Ayadi L, Ellouze S, Khabir A, Daoud E, Bahri I, Trigui D, Mnif Z, Beyrouti MI, Makni S, Boudawara T. Frantz's tumor: anatomoclinical study of six Tunisian cases. Rev Med Brux 2008; 29: 572-6 (in French).

606. Reddy S, Cameron JL, Scudiere J, Hruban RH, Fishman EK, Ahuja N, Pawlik TM, Edil BH, Schulick RD, Wolfgang CL. Surgical management of solid-pseudopapillary neoplasms of the pancreas (Franz or Hamoudi tumors): a large single-institutional series. J Am Coll Surg 2009; 208: 950-7.

607. Kang CM, Kim HK, Kim H, Choi GH, Kim KS, Choi JS, Lee WJ. Expression of Wnt target genes in solid pseudopapillary tumor of the pancreas: a pilot study. Pancreas 2009; 38: e53-9.

608. Matos JM, Grützmann R, Agaram NP, Saeger HD, Kumar HR, Lillemoe KD, Schmidt CM. Solid pseudopapillary neoplasms of the pancreas: a multi-institutional study of 21 patients. J Surg Res 2009; 157: e137-42.

609. Reddy S, Wolfgang CL. Solid pseudopapillary neoplasms of the pancreas. Adv Surg 2009; 43: 269-82.

610. Kim SH, Cho YT, Kwon HJ, An CM, Kim IH, Kim SW, Lee ST, Lee SO. A case of atypical solid-pseudopapillary tumor of the pancreas. Korean J Gastroenterol 2009; 54: 252-6 (in Korean).

611. Farah-Klibi F, El Amine O, Rammeh S, Ben Rejeb M, Ferchiou M, Kourda J, Abdessalem M, Zaouche A, Ben Jilani S, Zermani R. Solid pseudopapillary tumors of the pancreas: a pediatric case report. Tunis Med 2008; 86: 928-31 (in French).

612. Chung YE, Kim MJ, Choi JY, Lim JS, Hong HS, Kim YC, Cho HJ, Kim KA, Choi SY. Differentiation of benign and malignant solid pseudopapillary neoplasms of the pancreas. J Comput Assist Tomogr 2009; 33: 689-94.

613. Burford H, Baloch Z, Liu X, Jhala D, Siegal GP, Jhala N. E-cadherin/beta-catenin and CD10: a limited immunohistochemical panel to distinguish pancreatic endocrine neoplasm from solid pseudopapillary neoplasm of the pancreas on endoscopic ultrasound-guided fine-needle aspirates of the pancreas. Am J Clin Pathol 2009; 132: 831-9.

614. Kanter J, Wilson DB, Strasberg S. Downsizing to resectability of a large solid and cystic papillary tumor of the pancreas by single-agent chemotherapy. J Pediatr Surg 2009; 44: e23-5.

615. Terada T. Intraductal tubular carcinoma, intestinal type, of the pancreas. Pathol Int 2009; 59: 53-8.

616. 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.

617. van Wensen RJ, Bosscha K, Jager GJ, van der Linden JC, Fijnheer R. An invasive process in the pancreas: sometimes lymphoma. Ned Tijdschr Geneeskd 2009; 153: B164 (in Dutch).

618. Luo G, Jin C, Fu D, Long J, Yang F, Ni Q. Primary pancreatic lymphoma. Tumori 2009; 95: 156-9.

619. Yamagami Y, Ueshima S, Mizutani S, Uchikoshi F, Ohyama T, Yoshidome K, Tori M, Hiraoka K, Takahashi H, Sueyoshi K, Taira M, Kido T, Sakamaki Y, Yasukawa M, Oka K, Tsujimoto M, Nakahara M, Nakao K. An autopsied case of giant small cell carcinoma of the pancreas. Gan To Kagaku Ryoho 2009; 36: 123-5 (in Japanese).

620. Hurtuk MG, Hughes C, Shoup M, Aranha GV. Does lymph node ratio impact survival in resected periampullary malignancies? Am J Surg 2009; 197: 348-52.

621. Ghidirim G, Rojnoveanu G, Mişin I, Cernîi A, Gurghiş R. Carcinoid of the minor duodenal papilla associated with multiple jejunal leiomyomas in type 1 neurofibromatosis. Chirurgia (Bucur) 2009; 104: 491-4 (in Romanian).

622. Usuda A, Shiozawa S, Tsuchiya A, Kim DH, Usui T, Inose S, Aizawa M, Masuda T, Yoshimatsu K, Watanabe O, Katsube T, Naritaka Y, Ogawa K. Carcinoma of the ampulla of Vater arising from the peribiliary gland. Hepatogastroenterology 2009; 56: 1542-4.

623. Kuwakado S, Inoue T, Edagawa G, Fujii M, Ohgitani D, Tanaka T, Kii T, Moriguchi A, Kanemitsu N, Yoshida T, Kitae H, Kayano A, Suga K, Morita S, Ueno H, Egashira Y, Katsu K, Higuchi H. One case that accompanied accessory papilla carcinoid for von Recklinghausen's disease. Nippon Shokakibyo Gakkai Zasshi 2009; 106: 77-84 (in Japanese).

624. Merenda R, Portale G, Galeazzi F, Tosolini C, Sturniolo GC, Ancona E. Pancreaticoduodenectomy for dysplastic duodenal adenoma in a patient with familial adenomatous polyposis. Tumori 2008; 94: 882-4.

625. Lagoudianakis EE, Tsekouras D, Koronakis N, Chrysicos J, Archontovasilis F, Filis K, Katergiannakis V, Manouras A. A prospective comparison of ampullectomy with pancreaticoduodenectomy for the treatment of periampullary cancer. J BUON 2008; 13: 569-72.

626. Reddy S, Wolfgang CL. The role of surgery in the management of isolated metastases to the pancreas. Lancet Oncol 2009; 10: 287-93.

627. Medioni J, Choueiri TK, Zinzindohoué F, Cho D, Fournier L, Oudard S. Response of renal cell carcinoma pancreatic metastasis to sunitinib treatment: a retrospective analysis. J Urol 2009; 181: 2470-5.

628. Ion D, Sajin M, Copcă N, Pariza G, Mavrodin CI, Ciurea M. Late pancreatic metastasis from primary Grawitz tumor - surgical management. Chirurgia 2009; 104: 105-7 (in Romanian).

629. Cecka F, Jon B, Hatlová J, Tycová V, Neoral C, Ferko A, Melichar B. Renal cell carcinoma metastatic to the pancreas: a single center experience. Hepatogastroenterology 2009; 56: 1529-32.

630. Cecka F, Jon B, Hatlová J, Tycová V, Neoral C, Ferko A, Melichar B. Renal cell carcinoma metastatic to the pancreas: a single center experience. Hepatogastroenterology 2009; 56: 1529-32.

631. Volk A, Kersting S, Konopke R, Dobrowolski F, Franzen S, Ockert D, Grützmann R, Saeger HD, Bergert H. Surgical therapy of intrapancreatic metastasis from renal cell carcinoma. Pancreatology 2009; 9: 392-7.

632. Sperti C, Pasquali C, Berselli M, Frison L, Vicario G, Pedrazzoli S. Metastasis to the pancreas from colorectal cancer: is there a place for pancreatic resection? Dis Colon Rectum 2009; 52: 1154-9.

633. Walshe T, Martin ST, Khan MF, Egan A, Ryan RS, Tobbia I, Waldron R. Isolated pancreatic metastases from a bronchogenic small cell carcinoma. Ir Med J 2009; 102: 119-20.

634. Thirabanjasak D, Sosothikul D, Mahayosnond A, Thorner PS. Fibrolamellar carcinoma presenting as a pancreatic mass: case report and review of the literature. J Pediatr Hematol Oncol 2009; 31: 370-2.

635. Siderits R, Ouattara O, Abud A, Moubarak I, Mcintosh N, Godyn J. Retroperitoneal cystic abdominal lymphangiomatosis diagnosed by fine needle aspiration: a case report. Acta Cytol 2009; 53: 191-4.

636. Dim DC, Nugent SL, Darwin P, Peng HQ. Metastatic merkel cell carcinoma of the pancreas mimicking primary pancreatic endocrine tumor diagnosed by endoscopic ultrasound-guided fine needle aspiration cytology: a case report. Acta Cytol 2009; 53: 223-8.

637. Nagar AM, Raut AA, Morani AC, Sanghvi DA, Desai CS, Thapar VB. Pancreatic tuberculosis: a clinical and imaging review of 32 cases. J Comput Assist Tomogr 2009; 33: 136-41.

638. Dang S, Atiq M, Saccente M, Olden KW, Aduli F. Isolated tuberculosis of the pancreas: a case report. JOP 2009: 10: 64-6.

639. Avasthi R, Chaudhary SC, Jain P. Disseminated tuberculosis manifesting as chronic pancreatitis. Indian J Tuberc 2008; 55: 214-6.

640. Pandita KK, Sarla, Dogra S. Isolated pancreatic tuberculosis. Indian J Med Microbiol 2009; 27: 259-60.

641. Ke E, Patel BB, Liu T, Li XM, Haluszka O, Hoffman JP, Ehya H, Young NA, Watson JC, Weinberg DS, Nguyen MT, Cohen SJ, Meropol NJ, Litwin S, Tokar JL, Yeung AT. Proteomic analyses of pancreatic cyst fluids. Pancreas 2009; 38: e33-42.

642. Nealon WH, Bhutani M, Riall TS, Raju G, Ozkan O, Neilan R. A unifying concept: pancreatic ductal anatomy both predicts and determines the major complications resulting from pancreatitis. J Am Coll Surg 2009; 208: 790-9.

643. Brounts LR, Lehmann RK, Causey MW, Sebesta JA, Brown TA. Natural course and outcome of cystic lesions in the pancreas. Am J Surg 2009; 197: 619-22.

644. Gonzalez Obeso E, Murphy E, Brugge W, Deshpande V. Pseudocyst of the pancreas: the role of cytology and special stains for mucin. Cancer Cytopathol 2009; 117: 101-7.

645. Macari M, Finn ME, Bennett GL, Cho KC, Newman E, Hajdu CH, Babb JS. Differentiating pancreatic cystic neoplasms from pancreatic pseudocysts at MR imaging: value of perceived internal debris. Radiology 2009; 251: 77-84.

646. Ardengh JC, Coelho DE, Coelho JF, de Lima LF, dos Santos JS, Módena JL. Single-step EUS-guided endoscopic treatment for sterile pancreatic collections: a single-center experience. Dig Dis 2008; 26: 370-6.

647. Kim HC, Yang DM, Kim HJ, Lee DH, Ko YT, Lim JW. Computed tomography appearances of various complications associated with pancreatic pseudocysts. Acta Radiol 2008; 49: 727-34.

648. Tajima Y, Mishima T, Kuroki T, Kosaka T, Adachi T, Tsuneoka N, Kanematsu T. Huge pancreatic pseudocyst migrating to the psoas muscle and inguinal region. Surgery 2009; 145: 341-2.

649. Al-Ani R, Ramadan K, Abu-Zidan FM. Intrahepatic pancreatitic pseudocyst. N Z Med J 2009; 122: 75-7.

650. Coulier B, Maldague P, Bueres-Dominguez I. Spontaneous gastric drainage of a pancreatic pseudocyst. JBR-BTR 2009; 92: 61.

651. Dawson BC, Kasa D, Mazer MA. Pancreatic pseudocyst rupture into the portal vein. South Med J 2009; 102: 728-32.

652. Janík V, Pádr R, Keil R, Lischke R, Pafko P. Treatment of hemosuccus pancreaticus by bilateral embolization of gastric arteries. Cas Lek Cesk 2008; 147: 538-41(in Czech).

653. Massani M, Bridda A, Caratozzolo E, Bonariol L, Antoniutti M, Bassi N. Hemosuccus pancreaticus due to primary splenic artery aneurysm: a diagnostic and therapeutic challenge. JOP 2009; 10: 48-52.

654. Cherniavskiĭ AM, Karpenko AA, Starodubtsev VB. Surgical management of occlusion of the celiac trunk and an aneurysm of the inferior pancreatoduodenal artery.Angiol Sosud Khir 2009; 15: 115-7 (in Russian).

655. Endo K, Sata N, Shimura K, Yasuda Y. Pancreatic arteriovenous malformation: a case report of hemodynamic and three-dimensional morphological analysis using multi-detector row computed tomography and post-processing methods. JOP 2009; 10: 59-63.

656. Phelan HA, Velmahos GC, Jurkovich GJ, Friese RS, Minei JP, Menaker JA, Philp A, Evans HL, Gunn ML, Eastman AL, Rowell SE, Allison CE, Barbosa RL, Norwood SH, Tabbara M, Dente CJ, Carrick MM, Wall MJ, Feeney J, O'Neill PJ, Srinivas G, Brown CV, Reifsnyder AC, Hassan MO, Albert S, Pascual JL, Strong M, Moore FO, Spain DA, Purtill MA, Edwards B, Strauss J, Durham RM, Duchesne JC, Greiffenstein P, Cothren CC. An evaluation of multidetector computed tomography in detecting pancreatic injury: results of a multicenter AAST study. J Trauma 2009; 66: 641-6.

657. Montesano G, Zanella L, Favetta U, Del Bono P, Voccia L, Rossi FS. Rupture of the pancreatic isthmus due to blunt abdominal trauma. Chir Ital 2009; 61: 123-6 (in Italian).

658. Thomas H, Madanur M, Bartlett A, Marangoni G, Heaton N, Rela M. Pancreatic trauma – 12-year experience from a tertiary center. Pancreas 2009; 86: 113-6.

659. Gaines BA. Intra-abdominal solid organ injury in children: diagnosis and treatment. J Trauma 2009; 67 (2 suppl): S135-9.

660. Velmahos GC, Tabbara M, Gross R, Willette P, Hirsch E, Burke P, Emhoff T, Gupta R, Winchell RJ, Patterson LA, Manon-Matos Y, Alam HB, Rosenblatt M, Hurst J, Brotman S, Crookes B, Sartorelli K, Chang Y. Blunt pancreatoduodenal injury: a multicenter study of the Research Consortium of New England Centers for Trauma (ReCONECT). Arch Surg 2009; 144: 413-9.
661. Laituri C, Teixeira A, Lube MW, Seims A, Cravens J. Trauma laparotomy: evaluating the necessity of histological examination. Am Surg 2009; 75: 1124-7.

662. Ong SL, Garcea G, Pollard CA, Furness PN, Steward WP, Rajesh A, Spencer L, Lloyd DM, Berry DP, Dennison AR. A fuller understanding of pancreatic neuroendocrine tumours combined with aggressive management improves outcome. Pancreatology 2009; 9: 583-600.

663. Toyomasu Y, Fukuchi M, Yoshida T, Tajima K, Osawa H, Motegi M, Iijima T, Nagashima K, Ishizaki M, Mochiki E, Kuwano H. Treatment of hyperinsulinemic hypoglycemia due to diffuse nesidioblastosis in adults: a case report. Am Surg 2009; 75: 331-4.

664. Öberg K. Genetics and molecular pathology of neuroendocrine gastrointestinal and pancreatic tumors (gastroenteropancreatic neuroendocrine tumors). Curr Opin Endocrinol Diabetes Obes 2009; 16: 72-8.

665. Capelli P, Martignoni G, Pedica F, Falconi M, Antonello D, Malpeli G, Scarpa A. Endocrine neoplasms of the pancreas: pathologic and genetic features. Arch Pathol Lab Med 2009; 133: 350-64.

666. Landry CS, Waguespack SG, Perrier ND. Surgical management of nonmultiple endocrine neoplasia endocrinopathies: state-of-the-art review. Surg Clin North Am 2009; 89: 1069-89.

667. Åkerström G, Stålberg P. Surgical management of MEN-1 and -2: state of the art. Surg Clin North Am 2009; 89: 1047-68.

668. Gauger PG, Doherty GM, Broome JT, Miller BS, Thompson NW. Completion pancreatectomy and duodenectomy for recurrent MEN-1 pancreaticoduodenal endocrine neoplasms. Surgery 2009; 146: 801-6.

669. Shen HC, He M, Powell A, Adem A, Lorang D, Heller C, Grover AC, Ylaya K, Hewitt SM, Marx SJ, Spiegel AM, Libutti SK. Recapitulation of pancreatic neuroendocrine tumors in human multiple endocrine neoplasia type I syndrome via Pdx1-directed inactivation of Men1. Cancer Res 2009; 69: 1858-66.

670. Lejonklou M, Edfeldt K, Johansson TA, Stalberg P, Skogseid B. Neurogenin 3 and neurogenic differentiation 1 are retained in the cytoplasm of multiple endocrine neoplasia type 1 islet and pancreatic endocrine tumor cells. Pancreas 2009; 38: 259-66.

671. Dörffel Y, Wermke W. Neuroendocrine tumors: characterization with contrast-enhanced ultrasonography. Ultraschall Med 2008; 29: 506-14.

672. Borbath I, Jamar F, Delaunoit T, Demetter P, Demolin G, Hendlisz A, Pattyn P, Peeters M, Roeyen G, Van Cutsem E, Van Hootegem P, Van Laethem JL, Verslype C, Pauwels S. Diagnostic pitfalls in digestive neuroendocrine tumours. Acta Gastroenterol Belg 2009; 72: 29-33.

673. Verslype C, Carton S, Borbath I, Delaunoit T, Demetter P, Demolin G, Hendlisz A, Pattyn P, Pauwels S, Peeters M, Roeyen G, Van Hootegem P, Van Laethem JL, Van Cutsem E. The antiproliferative effect of somatostatin analogs: clinical relevance in patients with neuroendocrine gastro-entero-pancreatic tumours. Acta Gastrenterol Belg 2009; 72: 54-8.

674. He X, Wang J, Wu X, Kang L, Lan P. Pancreatic somatostatinoma manifested as severe hypoglycaemia. J Gastrointestin Liver Dis 2009; 18: 221-4.

675. Song S, Shi R, Li B, Liu Y. Diagnosis and treatment of pancreatic vasoactive intestinal peptide endocrine tumors. Pancreas 2009; 38: Aug 5 [Epub ahead of print].

676. Grobmyer SR, Vogel SB, McGuigan JE, Copeland EM, Hochwald SN. Reoperative surgery in sporadic Zollinger-Ellison Syndrome: longterm results. J Am Coll Surg 2009; 208: 718-22.

677. Mathur A, Gorden P, Libutti SK. Insulinoma. Surg Clin North Am 2009; 89: 1105-21.

678. Heni M, Schott S, Horger M, Dudziak K, Thamer C, Häring HU, Fritsche A, Müssig K. A rare cause of hypoglycaemia in a patient with type 2 diabetes. Dtsch Med Wochenschr 2009; 134 Suppl Falldatenbank F2 (in German).

679. Nakano K, Yamashita S, Soma I, Hayashi N, Higaki N, Murakami M, Hayashida H, Kan K, Ichihara T, Sakon M, Ayata M. A case of nonfunctioning islet cell tumor with extensive calcification. Nippon Shokakibyo Gakkai Zasshi 2009; 106: 1494-9 (in Japanese).

680. Pedicone R, Adham M, Hervieu V, Lombard-Bohas C, Guibal A, Scoazec JY, Chayvialle JA, Partensky C. Long-term survival after pancreaticoduodenectomy for endocrine tumors of the ampulla of Vater and minor papilla. Pancreas 2009; 38: 638-43.

681. Roeyen G, Chapelle T, Borbath I, Delaunoit T, Demetter P, Demolin G, Hendlisz A, Pattyn P, Pauwels S, Peeters M, Van Cutsemo E, Van Hootegem P, Van Laethem JL, Verslype C, Ysebaert D. The role of surgery and transplantation in neuroendocrine tumours. Acta Gastroenterol Belg 2009; 72: 39-43.

682. Matsubayashi H, Fukutomi A, Boku N, Uesaka K, Ono H. Diagnosis and treatment of pancreatic endocrine tumors. Gan To Kagaku Ryoho 2009; 36: 1611-8 (in Japanese).

683. Delaunoit T, Van den Eynde M, Borbath I, Demetter P, Demolin G, Pattyn P, Pauwels S, Peeters M, Roeyen G, Van Cutsem E, Van Hootegem P, Van Laethem JL, Verslype C, Hendlisz A. Role of chemotherapy in gastro-entero-pancreatic neuroendocrine tumors: the end of a story? Acta Gastroenterol Belg 2009; 72: 49-53.

684. Hendlisz A, Flamen P, Van den Eynde M, Borbath I, Demetter P, Demolin G, Pattyn P, Pauwels S, Peeters M, Roeyen G, Van Cutsemo E, Van Hootegem P, Van Laethem JL, Verslype C, Delaunoit T. Locoregional and radioisotopic targeted treatment of neuroendocrine tumours. Acta Gastroenterol Belg 2009; 72: 44-8.

685. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. Pancreas 2009; 38: 255-8.

686. Martin SK, Agarwal G, Lynch G. Subcutaneous fat necrosis as the presenting feature of a pancreatic carcinoma: the challenge of differentiating endocrine and acinar pancreatic neoplasms. Pancreas 2009; 38: 219-22.

687. Nissen NN, Kim AS, Yu R, Wolin EM, Friedman ML, Lo SK, Wachsman AM, Colquhoun SD. Pancreatic neuroendocrine tumors: presentation, management, and outcomes. Am Surg 2009; 75: 1025-9.

688. Sharma A, Muddana V, Lamb J, Greer J, Papachristou GI, Whitcomb DC. Low serum adiponectin levels are associated with systemic organ failure in acute pancreatitis. Pancreatology 2009; 9: 907-12.

689. Sakka N, Smith RA, Whelan P, Ghaneh P, Sutton R, Raraty M, Campbell F, Neoptolemos JP. A preoperative prognostic score for resected pancreatic and periampullary neuroendocrine tumours. Pancreatology 2009; 9: 670-6.

690. Vinik E, Carlton CA, Silva MP, Vinik AI. Development of the Norfolk Quality of Life Tool for assessing patients with neuroendocrine tumors. Pancreas 2009: 38: e87-95.