REVIEW OF LITERATURE ON CLINICAL PANCREATOLOGY

Scientific literature made available in the first half year of 2012

Selected and edited by Åke Andrén-Sandberg

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. Since a few years I have made consecutive quarterly reviews in an effort to make the reviewer myself 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 me, and other reviewers should probably have made at least some other choises. This is not all there is written in clinical pancreatology during this time period – but not far from it.

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 only some of the articles have been read in their full length, and 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 clinical pancreatology in the first half of 2012".

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 others 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 pancreas) 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 of a new paradigm – other may represent the reverse.

The plan is to follow this quarter by a new review next quarter 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, please let me hear your comments – but if the comments fail to appear, the next quarters and year will have the same disposition as the present. Welcome back next quarter!

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CONTENT

Reviewer's preface (and search algoritm)

ABBREVIATIONS

ANATOMY AND ANOMALIES

Pancreatic volume Different cell masses Patency of accessory pancreatic duct Common bile duct size Arterial variability Celiac artery stenosis Lymphatic drainage Annular pancreas Portal annular pancreas Agenesia of dorsal pancreas Heterotopic pancreas In the gall-bladder In esophagus Duodenal obstruction In jejunum In mediastinum Anomalous union of the pancreatico-biliary duct Intrapancreatic accessory spleen (splenunculus) Epithelial inclusion cyst arising within an intra-pancreatic splenunculus

PHYSIOLOGY

Purinergic signaling

Neural regulation of the pancreas Pancreatic vasculature Ecto-nucleotidases Pancreatic acini Pancreatic ducts Pancreatic stellate cells

Bicarbonate Pancreatic juice secretion Apelin Insulin protection of pancreatic acinar cells Pancreatic pain

DIABETES

Hyperinsulinemia Glucagon

ENDOSCOPY

A protocol for biliary cannulation ERCP-related duodenal perforations Endoscopic ultrasonography (EUS) Secretin stimulation at endoscopic ultrasound EUS-FNA EUS-guided transluminal cholangiodrainage (EUCD) EUS-guided anterograde cholangiopancreatography in failed ERCP EUS-guided elastography Self-expandable metal stent placement Colonization of pancreatic stents

OTHER DIAGNOSTICS

CT Diffusion-weighted imaging (DWI) Secretin-enhanced MRCP Proton magnetic resonance spectroscopy Ultrasound based acoustic radiation force impulse (ARFI)

ACUTE PANCREATITIS

Background to revision of Atlanta classification The revised Atlanta classification of acute pancreatitis Scoring system Blood glucose as predictor of severity Guidelines Epidemiology Importance of age Diagnostics MRI Smoking SPINK-1 Cytokines Moderately severe acute pancreatitis Acute biliary pancreatitis Timing of cholecystectomy after mild biliary pancreatitis Prediction for recurrence Early cholecystectomy and ERCP EST and stenting Laparoendoscopic rendezvous versus preoperative ERCP Acute alcoholic pancreatitis Experimental Post-ERCP-pancreatitis Rectal indometacine as prophylaxis Low dose heparin Triglceride-induced acute pancreatitis Plasmapheresis Experimental Outflow obstruction acute pancreatitis Due to pancreatic hydatid cyst **IPMN** Anomalous pancreaticobiliary junction Duodenal diverticula Drug-induced acute pancreatitis Sitagliptin Hypthermia-induced acute pancreatitis Dialysis-induced acute pancreatitis Vascular complications of pancreatitis Endovascular stenting Diabetes Coagulation Parathyroid hormone In Wegener's granulomatosis Schnitzler's syndrome Disconnected pancreatic duct syndrome

Early enteral feeding

Treatment with daptomycin

Antibiotics

Peripancreatic fluid collections

Pancreatic necrosis

Diagnosis Interventions Endoscopic transgastric versus surgical necrosectomy Step-up strategy EUS-guided endoscopic necrosectomy Retroperitoneal laparoscopic necrosectomy Late sequelae Pulmonary embolism

Abdominal compartment syndrome

Nutrition

Case reports

Dyspareunia Cannabis and acute pancreatitis Panniculitis

Experimental

Impact of age Infliximab

CHRONIC PANCREATITIS

Epidemiology

In Asia

Genetics

Mismatch excision repair (MMR) Proteomic analysis Intrapancreatic blood flow In liver cirrhosis Focal pancreatitis Pancreatic function in diabetes Antioxidants Pain Surgery Pancreaticoduodenectomy Pancreaticoduodenectomy versus duodenum-preserving pancreatic head resection Total pancreatectomy and islet autotransplantation Robot-assisted pancreatoduodenectomy Surgery versus endoscopic pain treatment Bilateral thoracoscopic splanchnicectomy Pancreatopleural fistulae Pancreas divisum MRCP **AUTOIMMUNE PANCREATITIS**

Overviews

A systemic disease

Epidemiology

In Japan Biopsy of non-pancreatic organs

Diagnostics

PET/CT

Immunoglobulins

Regulatory T-cells Population IgG4 IgG4 and extrapancreatic lesions

Addresins

Insufficiencies Glucos intolerance Exocrine insufficiency Differentiation against pancreatic adenocarcinoma Differential diagnosis Concomitant symptoms and diseases With cholangitis Sclerosing cholangitis Sclerosing sialadenitis Bronchial asthma preceding IgG4-related autoimmune pancreatitis Sjögren syndrome Pachymeningitis and tracheobronchial stenosis Nephropathy

HEREDITARY PANCREATIC DISEASES

Overview BRCA 1 and BRCA 2 Familial pancreatic cancer Hereditary hemorrhagic telangiectasia Johanson-Blizzard syndrome Peutz-Jeghers syndrome

STELLATE CELLS

Overview Histology

Hepatic and pancreatic stellate cells Stem cells? Pancreatic cancer stem cells Isolation Activation Stellate cells versus fibroblasts Species variance During pancreatic injuriy Intratumorally L-cysteine Galactin In senescence

PANCREATIC CANCER

Overview Epidemiology Germany USA Puerto Rico Time trend regarding incidence Time trend regarding mortality Etiological agens, risk factors and proposed risk factors After acute pancreatitis Smoking Hepatitis B

Radiation Cruciferous vegetables (cabbage) Red meat Polycyclic aromatic hydrocarbons Physical activity Obesity Cholesterol Diabetes IGF-1 Proton pump inhibitor Vitamin D Vitamin C and E Cadmium Inorganic lead Metal industry Oral microbiota Covariation with other cancer Covariation with chronic obstructive pulmonary disease Hypertension Helicobacter Molecular biology Molecular markers in general Proteomics Adiponectin Angiogenesis Cell adhesion molecules C-terminal tensin-like gene (CTEN) EGFR Fibers HSP70 Hyperfucosylated lactosamines IGF-1 Lymphangiogenesis miRNAs M2-polarized tumor-associated macrophages mRNA mtDNA Mucines Myeloid-derived suppressor cells (MDCD) Osteopontins Poly-(ADP-ribose)-polymerases (PARPs) SLC5A8 Smac and Ki-67 Sonic hedgehog Sleeping beauty mutagenesis Superoxide Syndecan-2 Tregs Tumor-associated macrophages (TAMs) Biomarkers for pancreatic cancer Other (traditional) tumor markers Experimental Influence of stress Genetics **BRCA1 and BRCA2**

PRSS1 ABO-groups 6q13 Histopathology On the origin of "ductular" cancer Post-therapy pathologic stage Morphometrical differences Borderline cases **Precancerous lesions** Nonlinear optical methods Dendritic cells Symptoms and signs Double duct sign Sarcoid-reaction Superficial venous thrombosis Energy expenditure Mestastases from pancreas Incidentalomas At screening Diagnostics for pancreatic cancer EUS Contrast-enhanced EUS CT and MDCT PFT PET-CT MRI Nuclear magnetic resonance spectroscopy Cytology EUS-guided FNA Brush cytology Cytodiagnostic endoscopic nasopancreatic drainage CEA Radiofrequency spectral parameters Screening for pancreatic cancer High-risk individuals Preoperative management Anesthesiology Surgical overview Minimal invasive pancreatic surgery (laparoscopy) Organisation of surgery Low-volume versus high-volume hospitals Health related transitions Personalised medicine Cooperation between hospitals Early cancer Speed of growth Perioperative prognosis Surgical Apgar score Staging laparoscopy Surgical techniques Pancreatojejunostomy Pancreatogastrostomy Experimental pancreaticojejunostomy Proximal gastrojejunal reconstruction Pancreatoduodenectomy in patients with liver cirrhosis

Total pancreatectomy Total mesopancreas excision (TMpE) Central pancreatectomy Tumors of the neck of the pancreas with venous invasion Extended lymph node resection Hepatic artery reconstruction Preservation of the posterior epiploic artery Preoperative embolization of replaced right hepatic artery Portal vein resection External stent drainage of the pancreatic duct Laparoscopy Robot-assisted pancreaticoduodenectomy Bipolar radiofrequency in parenchymal transection Adrenalectomy Cancer of the body and tail Presenting symptom Distal pancreatectomy Antegrade modular pancreatosplenectomy procedure Appleby operation (including celiac axis) Laparoscopic resection Margins Chyle leak Other postoperative complications Survival Postoperative care Physical training Discharge after pancreatic resection Postoperative complications Post-pancreatectomy bleeding Pancreatic fistula **Prognostic factors** Japanese registry Metastatic lymph node ratio Perineural invation Peritumoral lymphatic vessel density Lymphovascular invasion Uncinate process pancreatic cancer Lymph node metastases in relation to cancer from ventral versus dorsal anlage Postoperative hepatic steatosis Age Scores Adrenalectomy Microvessel density in lymph node metastasis EGFR D-dimer CA 19-9 Prognostic biomarkers Diabetes after pancreatic resection Pancreatic neoplasms during pregnancy First trimester Second trimester Third trimester Unresectable tumors during pregnancy Population-based results USA

Norway Local recurrence Venous thrombosis Portal hypertension Long-term survival Palliative resection Other palliation Surgical interventions Endoscopic stenting versus operative gastrojejunostomy Quality of life Depression Neoadjuvants before radically intended surgery In borderline patients Chemoradiotherapy Complete response Predictive factors for recurrence Adjuvants to radical surgery Carbon-ion radiotherapy (CIRT) Adjuvants to radical surgery Hyperthermic intraperitoneal intraoperative chemotherapy Pharmacological therapy generalized disease Overview Gemcitabine Gemcitabine and oxaliplatin Gemcitabine, docetaxel and capecitabine (GTX) Gemcitabine and capcitabine plus docetaxel (PDXG) or epirubicne (PEXG) Gemcitabine, cisplatin and erlotinib (GPT) FOLFIRINOX Gemcitabine, oxaliplatin, 5FU and conformal radiotherapy **Bevacizumab** Erlotinib Guggulstrone and gemcitabine G17DT Triptolide Drug-delivery by nanotechnology Second line therapy Experimental Radiotherapy Radiotherapy planning Dosimetry Tumor volume as predictor of effect Adjuvant proton therapy Stereotactic body radiation therapy Combined with gemcitabine and erlotinib Intensity-modulated radiotherapy (IMRT) Intratumoural treatment Cost-effectiveness Other non-surgical, non-pharmacological treatments of pancreatic cancer Crvoabladation Irreversible electroporation therapy Experimental MRI Stromal inflammatory cells Surviving pancreatic cancer cells after exposure to gemcitabine or 5-fluorouracil Zoledronic acid

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Overview Natural history Proteomics of mucous Histopathology Multifocality Subtypes Imaging EUS MRI **Differential diagnosing** Immunobiology Familary and hereditary IPMNs Labelling index Slow growth Branch duct type intraductal papillary mucinous neoplasm **Evaluation with MDCT** Mixed duct type intraductal papillary mucinous neoplasm Main duct IPMN Simultaneous intraductal papillary neoplasms of the bile duct and pancreas Concomitant with pancreatic cancer Complications to IPMN Imaging Penetrating the stomach Recurrent acute pancreatitis IPMN and aortic aneurysm Mucin intraperitoneally Enucleation Prognostic factors Branch duct IPMN Impact of positive margins and lymph gland involvement Extrapancreatic malignancies Surgery Pylorus- and spleen-preserving total pancreatoduodenectomy Fate of the pancreatic remnant after resection Recurrence **Biliary IPMN** Photodynamic therapy of intraductal papillary mucinous neoplasm OTHER CYSTIC PANCREATIC TUMORS Incidence Rate of growth

Rate of growth Diagnostics Cyst fluid analysis Contrast-enhanced ultrasound CT MRI High-resolution optical imaging Immunohistochemistry Microcystic adenoma Growth rate Serous cystadenoma Serous cystadenoma coexistent with adenosquamous carcinoma Solid cystic serous adenoma Serous cystadenocarcinoma Mucinous cystadenoma Mucinous cystadenoma of the mesocolon von Hippel-Lindaus disease Incidental pancreatic cysts Nonneoplastic mucinous cysts

NON-PANCREATIC PERIAMPULLARY CANCER

Duodenum

Cancer GIST Familial adenomatous polyposis Inflammatory myofibroblastic tumours (IMT) Papilla of Vater Pancreas-sparing duodenectomy (PSD) Annular pancreas Endoscopic ampullectomy Lower bile duct Adenosquamous carcinoma of lower extrahepatic bile duct

OTHER RARE PANCREATIC TUMORS

Imaging features of the less common pancreatic masses Selected case materials Double pancreatic cancers Large duct type invasive adenocarcinoma Acinar cell carcinoma A novel antibody **Cytostatics** Primary retroperitoneal acinar cell cystadenoma Of the stomach Adenosquamous carcinoma Solid pseudopapillary neoplasms (SPN) Clear cell variant Two types Immunohistochemistry Contrast-enhanced US Surgery Peritoneal carcinosis Late recurrence Small cell carcinoma Colloid carcinoma Choriocarcinoma Intraductal tubulopapillary neoplasm Hepatoid cancer Hematological malignancies involving pancreas Granulocytic sarcoma (choloroma) Extramudullary plasmocytoma PEComa Lymphangioleiomyomatosis Lymphoid hyperplasia Castleman's disease Teratoma Cystic

GIST Schwannoma Neurofibroma Inflammatory pseudotumor Lymphoepithelial cysts Pancreatic amyloidosis Metastases to pancreas Fine needle biopsy Surgery From kidney From urinary bladder From thyroid From uterus From leiomyosarcoma Metastase from pancreatic cancer To inner genitalia

PANCREATIC ENDOCRINOLOGY AND ENDOCRINE TUMORS

Guidelines Genomics Staging systems Diagnostics MRI Chromogranin A ⁶⁸Ga-DOTA-TOC

Insulinoma VIP and calcitonin-producing pancreatic tumor MEN 1 Cystic pancreatic endocrine neoplasms Extended surgery

CHILDREN

Diagnostics Pancreatic autoantibodies Acute pancreatitis Laparoscopic necrosectomy Chronic pancreatitis Etiology Octreotide treatment Pancreatic solid tumors Pancreatoblastoma Pancreatic cystic tumors Primary pancreatic lymphoma Pancreatic pseudocysts Pancreatic aneurysms Trauma Seat-belt trauma

PSEUDOCYSTS AND PSEUDOANAEURYSMS

Overview of pseudocysts Pseudocysts after acute pancreatitis Mediastinal pseudocyst Splenic pseudocyst Intramural duodenal pseudocyst Pseudocyst of the pancreas in a pregnant patient. EUS-guided scanning Endoscopic treatment EUS-guided Complication to treatment Self expandable metallic stent In HIV/AIDS A risk factor for pancreatic cancer Bleeding A giant pseudocyst Mediastinal pseudocyst Concomitant pseudocyst and pseudoanaerysm Trombin injections in a posttraumatic aneurysm Experimental Pancreatic pseudoaneurysm Transarterial embolization

PANCREATIC TRAUMA

Incidence of pancreatic trauma Management algoritm Amylas and lipase for diagnosis Intramuscular autologous islet transplantation for traumatic transection Penetrating injuries Blunt trauma Endoscopic treatment Surgery Effect of splenectomy on blood glucose Biliary tract trauma

TRANSPLANTATION

Islet transplantation Purification of islets Effects of digestion enzymes on islet viability Laparoscopic robot-assisted pancreas transplantation Long-term survival Tacrolimus-induced pancreas injury

PANCREATIC NUTRITION

Probiotics Omega-3 long-chain polyunsaturated fatty acids Enteral feeding patients with gastric outlet obstruction Vegan diet

PANCREATIC INFECTIONS

HIV Herpes simplex Tuberculosis Tuberculosis and HIV Hydatide infection

REFERENCES

ABBREVIATIONS

AACT	alpha 1-antichymotrypsin
AAL	Aleuria aurantia lectin
AASLD	American Association for the Study of Liver Diseases
AAST	American Association for the Surgery of Trauma
ABP	acute biliary pancreatitis
ACC	acinar cell carcinomas
ACE	accelerating coagulation extent
Ach	acetylcholine
ACP	pancreatic adenocarcinoma
ACS	American Cancer Society
ACTH	adrenocorticotrophic hormone
ADC	apparent diffusion coefficients
ADM	acinar-ductal metaplasia
ADR	adverse drug reactions
ADX	adrenalectomy
AFE	accelerating fibrinolytic extent
AIP	autoimmune pancreatitis
AJ	Ashkenazi Jewish
AJCC	American Joint Committee on Cancer
ALDH2	aldehyde dehydrogenase 2 gene
ALG	algorithm
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANP	acute necrotizing pancreatitis
AP	acute pancreatitis
AP	annular pancreas
APACHE	Acute Physiology and Chronic Health Evaluation
APBJ	anomalous pancreaticobiliary junction
APC	advanced pancreas cancer
APC	argon plasma coagulation
APD	accessory pancreatic duct
APFC	acute peripancreatic fluid collections
APN	acute necrotizing pancreatitis
AR/CP	acute recurrent or chronic pancreatitis
ARFI	acoustic radiation force impulse
ART	antiretroviral therapies
ART	adaptive radiotherapy
ASCA	antibodies against Saccharomyces cerevisiae
ASR(E)	age-standardised incidence rates (per 100,000 European standard population)
AST	aspartate aminotransferase
AUC	area under the curve
AUPBD	anomalous union of the pancreatico-biliary duct
AWR	absolute washout rate
BaP	benzo(a)pyrene
BC	breast cancer
BD-IPMN	branch duct intraductal papillary mucinous neoplasms
BH	breath-holding
BH-IMR	breath-holding intensity-modulated radiotherapy
B-IPMN	biliary intraductal papillary mucinous neoplasm
BISAP	bedside index for severity in acute pancreatitis
BLE	balance level exponent
BM	bone marrow

BMI	body mass index
BNCN	benign, noncommunicating cystic neoplasms
BOP	N-nitrosobis (2-oxopropyl) amine
BRCPa	borderline resectable pancreatic cancer
BTS	bilateral thoracoscopic splanchnicectomy
BV	blood volume
CA	celiac artery
CA	carbohydrate antigen
	chronic alcohol exposition
	common bilo duot
CBD	
	candidate cancer genes
CCK	cholecystokinin
CCRS	complete cytoreductive surgery
CCRT	concurrent chemoradiation therapy
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CEA	carcinoembryonic antigen
CE-CT	contrast-enhanced computed tomography
CED	coverage-with-evidence-development
CE-EUS	contrast-enhanced harmonic endoscopic ultrasonography
CEM	confocal endomicroscopy
CEUS	contrast-enhanced ultrasound
CFH	complement factor H
CETR	cystic fibrosis transmembrane conductance regulator
Cho	choline
	confidence intervals
	confidence intervals
	carbon-ion radiomerapy
	cylokeralin
	circulating lymphold dendritic cells
CIOFAL	clot formation and lysis
c-m-DC	circulating myeloid dendritic cells
CMV	cytomegalovirus
CNS	central nervous system
CNV	copy number variant
COPD	chronic obstructive pulmonary disease
CP	chronic pancreatitis
CP	clinical pathway
CP	cystadenomas of the pancreas
CPC	cerebral performance categories
CPEN	cystic pancreatic endocrine neoplasms
CSEMS	covered self expandable metallic stent
CSC	cancer stem cells
CT	computed tomography
CT	coagulation time
	computed tomography angiography
CTC	computed tomography anglography
	C-terminal tensin-like gene
	C i severity index
	ciinicai target voiume
	auodenai adenocarcinoma
DaRT	diffusing alpha-emitters radiation therapy
DBP	vitamin D binding protein
DC	dendritic cells

DCA	ductal adenocarcinoma
DCR	disease control rate
3DCRT	three-dimensional conformal radiotherapy
DD	duodenal diverticula
DDP	cisplatin
DF	dual-energy
DFI	disease free interval
	digital image analysis
	2 amino 2 4 8 trimothylimidazo[4 5 flauinovalino
DLO	
DIVI	
DP	distal pancreatectomy
DPDS	disconnected pancreatic duct syndrome
DPPC	double primary pancreatic cancer
DPPHR	duodenum-preserving pancreatic head resection
DR	distant recurrence
DRG	diagnosis-related groups
DU	duodenal ulcers
DW	diffusion-weighted
DWI	diffusion-weighted imaging
DW-EPI	diffusion-weighted echo-planar imaging
EACP	EUS-guided anterograde cholangiopancreatography
EBRT	external beam radiotherapy
EBV	Epstein-Barr virus
E-CG	endoscopic cyst gastrostomy
ECIPAS	epidermoid cyst involving intrapancreatic cyst
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
EE	end-exhalation
EGIST	extragastrointestinal stromal tumor
EMR	endoscopic mucosal resection
EMT	epithelial mesenchymal transition
ENETS	European Neuroendocrine Tumor Society
ENI	elective nodal irradiation
ENPD	of endoscopic nasopancreatic drainage
EP	extrapancreatic score
EpCAM	epithelial cell adhesion molecule
ePFT	endoscopic pancreatic function test
EPIC	extrapancreatic inflammation on CT score
EPL	extrapancreatic lesions
EPM	extrapancreatic malignancies
Epo	erythropoietin
ERCP	endoscopic retrograde cholangiopancreaticography
ERP	endoscopic retrograde pancreatography
EST	endoscopic sphincterotomy
ET	endocrine tumor
EUCD	endoscopic ultrasonography-guided cholangiodrainage
EUS	endoscopic ultrasonography
EUS-FNA	endoscopic ultrasound-guided fine-needle aspiration
EUS-PPD	endoscopic ultrasound guided pancreatic pseudocvst drainage
FAD	flavin adenine dinucleotide
FAP	familial adenomatosis polyposis
FB	free breathing
FC	flow cytometry
FCPL	focal cystic pancreatic lesion
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FDG	fluorodeoxyglucose
FH	family history
FISH	fluorescence in situ hybridization
FLT	fluorothymidine
fMRC	functional magnetic resonance cholangiography
FNA	fine-needle aspiration
FOI FIRINO	infusional 5-fluorouracil/folinic acid plus irinotecan and oxaliplatin
FP	focal pancreatitis
FPC	familial pancreatic cancer
FT	fibrinolysis time
F/11	follow-up
F/U	follow-up
	5 fluerouroeil
J-FU	o-nuorouracii reblet eelle entibedu
GAB	gobiet cells antibody
GABA	
CAMP	cyclic adenosine 3, 5-monophosphate
nAChR	nicotinic acetylcholine receptors
GCKR	glucokinase regulator
GDA	gastroduodenal artery
GEM	genetically engineered mouse
GEP	gastroenteropancreatic
GIST	gastrointestinal stromal tumors
GLI	glycemic lability index
G4-Ps	IgG4-positive plasma cells
GPT	gemcitabine, cisplatin, and erlotinib
GRAD	maximum ascending gradient
GTV	gross tumor volume
GTX	gemcitabine, docetaxel and capecitabine
Gy	gray
GyE	grays equivalents
FDG-PET-C	I ¹⁸ F-fluoro-deoxy-D-glucose positron emission tomography-CT
HA	hepatic artery
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCA	heterocyclic amines
HCV	hepatitis C virus
H&E	hematoxylin and eosin
HEV	high endothelial venule
ННТ	hereditary haemorrhagic telangiectasia
HIPC	hyperthermic intraperitoneal chemotherapy
HIPEC	hyperthermic intraoperative intraperitoneal chemotherapy
HIV	human immunodeficiency virus
¹ H MRS	proton magnetic resonance spectroscopy
HPP	human pancreatic polypeptide
HR	hazard ratio
HRG	histidine-rich alvcoprotein
HRI	high-risk individuals
HSC	hepatic stellate cells
HSP	heat shock protein
HSV	herpes simplex virus
HU	Hounsfield units
IAC	InG4-associated cholangitis
IAI	intra-abdominal injury
IAT	islet autotransplantation

IBD	inflammatory bowel disease
ICC	intraclass correlation coefficient
ICDC	international consensus diagnostic criteria
ICER	incremental cost-effectiveness ratio
ICG	indocyanine green
ICOS	inducible costimulatory molecule
ICU	intensive care unit
IDE	investigational device exemption
IFN	interferon
IGF-1	insulin-like growth factor 1
IGFBP-3	binding protein insulin-like growth factor 3
lgG4	immunoglobulin G4
IgG4-RD	immunoglobulin G4-related disease
IgG4-RSD	immunoglobulin G4-related systemic disease
IĞRT	image-guided radiotherapy
IL	interleukin
ILK	integrin-linked kinase
iLVD	intra-tumoral lymphatic vessel density
IMRT	intensity-modulated radiotherapy
IMS	imaging mass spectrometry
IMT	inflammatory myofibroblastic tumours
IN	image noise
IPAS	intrapancreatic accessory spleen
IPDA	inferior pancreaticoduodenal artery
IPMN	intraductal papillary mucinous neoplasm
IPMN-B	intraductal papillary mucinous neoplasms of the bile duct
IPMN-P	intraductal papillary mucinous neoplasms of the pancreas
IPNB	intraductal papillary neoplasm of the bile duct
IQ	image quality
IRF	irreversible electroporation
ISD	InG4-associated systemic disease
ISGPE	International Study Group on Pancreatic Fistula
IUGR	intrauterine growth restriction
IAM	lymphangioleiomyomatosis
LAPC	locally advanced pancreas cancer
	local complications
	local control
LC-MS-MS	liquid chromatography coupled to tandem mass spectrometry analysis
	Lieber-DeCarli (a diet)
IDP	Japaroscopic distal pancreatectomy
LEC	lymphoenithelial cysts
	Janaroendosconic rendezvous
Lin	linid
IN	lymph node
	lymph node metastasis
	loss of heterozyaosity
	lanarosconic pylorus-preserving pancreaticoduodenectomy
IRPES	local-regional progression-free survival
	lymnhatic vessel density
	low-volume hospitals
	lymphovascular invasion
MA	maximum amplitude
MACC	Iomustine
	mucosal addressin cell adhesion molecule
	madian arcuate ligament

MALDI	matrix-assisted laser desorption/ionization
MBO	malignant biliary obstruction
MCN	mucinous cystic neoplasms
MCP	metastatic cancer to the pancreas
MCTSI	modified CT severity index
MD	Mikulicz's disease
MDCT	multidetector-row computed tomography
MDSC	myeloid-derived suppressor cells
MelQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
MEN 1	multiple endocrine neoplasia type 1
MGL	mean glucose level
miRNA	microRNA
MMP	matrix metalloproteinase
MMR	mismatch excision repair
MN	mural nodule
MODY3	maturity onset diabetes of the young type 3
MOP	mesenteric oedema and peritoneal fluid score
MOR	maximum overlap ratio
MPC	metastatic pancreatic adenocarcinoma
MPD	main pancreatic duct
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreaticography
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRS	proton magnetic resonance spectroscopy
MSAP	moderately severe acute pancreatitis
MSCA	microcystic serous cystadenomas
MSCT	multi-slice computed tomography
mtDNA	mitochondrial DNA
m/z	mass-to-charge ratio
MUC	mucin
MVD	microvessel density
NA	noradrenaline
NAACCR	North American Association of Central Cancer Registries
nAChR	nicotinic acetylcholine receptor
NAD(P)H	nicotinamide adenine dinucleotide (phosphate)
NBCÀ	N-butyl cyanoacrylate
NCI	National Cancer Institute
NCRT	neoadjuvant chemoradiotherapy
NET	neuroendocrine tumor
NETP	neuroendocrine tumors of the pancreas
NF	neurofibromatosis
NG	nasogastric
NGAL	neutrophil gelatinase-associated lipocalin
NHL	non-Hodgkin's lymphomas
NJ	nasojejunal
NOC	Nal3-octreotide
NOM	nonlinear optical microscopy
NOX2	NADPH oxidase-2
NP	nanoparticles
NPV	negative predictive value
NSE	neuron-specific enolase
OAR	organs at risk
OCT	optical coherence tomography
ODA	ordinary ductal adenocarcinoma

ODP	open distal pancreatectomy
OF	organ failure
25(OH)D	25-hydroxyvitamin D
OR	odds ratio
ORR	overall response rate
03	
OSM	oncostatin M
PA	pancreas adenocarcinoma
PAB	exocrine pancreas antigen
PAH	polycyclic aromatic hydrocarbons
PAI	plasminogen activator inhibitor
pANCA	perinuclear components of neutrophils
PanIN	pancreatic intraepithelial neoplasia
PAP	Portal annular pancreas
PARP	nolv-(ADP-ribose)-nolvmerase
DRI	pancroatoblastoma
	particealle-billary juice
PBIVI	pancreaticobiliary maiformation
PC	pancreatic cancer
PCD	percutaneous catheter drainage
PCL	pancreatic cystic lesions
PCM	pancreatic cystic mass
PCR	polymerase chain reaction
pCR	pathologic complete response
PD	pancreaticoduodenectomy
PD	pancreatic duct
PD	peritoneal dialysis
PDA	pancreatic ductal adenocarcinomas
	pancreatic ductal adenocarcinoma
	platelet-derived growth factor recentor alpha
	platelet-derived growth factor feceptor alpha
	priotodynamic therapy
PDXG	gemcitabin, capcitabine and docetaxei
PEA	posterior epiploic artery
PEComa	perivascular epithelioid cell tumors
PEI	pancreatic exocrine insufficiency
PEI	peak enhancement intensity
PET	positron emission tomography
PEXG	gemcitabin, capcitabine and epirubicne
PF	pancreatic fistula
PF	perfusion
PFB	pancreatic fibroblasts
PFS	progression-free survival
PG	pancreaticogastrostomy
PG	parotid gland
PGI	provimal aastroieiunostomy
	proximal gastrojejunostomy
	Dereand Health Questionnaire 0
	peak intensity
P-IPMIN	pancreatic intraductal papillary mucinous neoplasm
rj	pancreaticojejunostomy
PLVD	peri-tumoral lymphatic vessel density
PMCA	piasma membrane Ca ²⁺ -A I Pase
PMP	pseudomyxoma peritonei
pNET	pancreatic neuroendocrine tumor

PNI	perineural invasion
PNT	pancreatic neuroendocrine tumor
PNPFC	post-necrotic pancreatic/peripancreatic fluid collections
POPF	postoperative pancreatic fistula
PPC	pancreatic pseudocvst
PPI	primary pancreatic lymphoma
	pylorus-preserving pancreaticoduodenectomy
DoSoTDD	pylorus-preserving panorealicoudodenectomy
DDES	pylorus- and spieen-preserving total paneteatoddodenectomy
PDECO	
PRESS	point-resolved selective spectroscopy sequence
PR551	cationic trypsinogen
PPV	positive predictive value
PRV	pancreatic remnant volume
PS	pilonidal sinus
PSC	pancreatic stellate cells
PS	pancreatic stents
PSC	pancreatic stellate cells
PSD	pancreas-sparing duodenectomy
PSI	pancreatic size index
PSWQ	Penn State Worry Questionnaire
PT	proton-based radiotherapy
PTC	papillary thyroid cancer
PTHrP	parathyroid hormone-related protein
PTV	planning target volume
Pty	pentovifulline
	portal voin
	von Hinnel Lindeu gene preduct
	von Ripper-Lindau gene product
PV-5IVIV	ponal vein-superior mesenteric vein
qPCR	real-time quantitative PCR
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
QUALY	quality-adjusted life years
RA	retinoic acid
RAC	recurrence in the abdominal cavity
RAI	radioactive iodine
RAMPS	radical antegrade modular pancreatosplenectomy
RAPD	robot-assisted pancreaticoduodenectomy
RBP-4	retinol binding protein 4
RCC	renal cell carcinoma
RCT	randomized controlled trials
REE	resting energy expenditure
RF	radiofrequency
RHA	right henatic artery
RIH	reactive lymphoid hyperplasia
	regional lymph node
	receiver enerating characteristic
	region of interest
RUI	
IPAB	recombinant pancreas antigens
RI	radiotherapy
RIUG	Radiation Therapy Oncology Group
RT-PCR	real-time reverse transcriptase polymerase chain reaction
RWR	relative washout rate
SAA	serum amyloid A
SA beta-Gal	senescence-associated beta-galactosidase
SAO	serous oligocystic adenoma
SAP	severe acute pancreatitis

SAP	splenic artery pseudoaneurysms
SAR	survival after recurrence
SAS	surgical Apgar score
SB	sleeping beauty
SBRT	stereotactic body radiation therapy
SC	sclerosing cholangitis
SCC	small cell carcinoma
SCCP	small cell carcinoma of the pancreas
SCA	serous cystadenoma
SCN	serous cystadenoma
SON	servide cystic neoplasitis
SDC	Synuciality and the senser calls
SDCC	
	Single-energy
SEER	Surveillance Epidemiology and End Results
SEMS	self-expandable metal stent
SES	socioeconomic status
sEUS	secretin stimulated endoscopic ultrasound
SF-36	36-item Short Form
SHG	second harmonic generation
SHH	sonic hedgehog
SIR	standardized incidence ratio
siRNA	interfering RNA
SMA	serous microcystic adenomas
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNP	single nucleotide polymorphism
SPARC	secreted protein acidic and rich in cysteine
SPC	subsequent primary cancer
SPDP	spleen-preserving distal pancreatectomy
SPH	sinistral portal hypertension
SPINK1	serine protease inhibitor Kazal type 1
SPM	second primary malignancies
SPN	solid pseudopapillary neoplasms
SPTP	solid-pseudopapillary tumor of pancreas
SS	Sjögren's syndrome
SSCA	solid serous cystadenoma
SSTR	somatostatin receptor
STZ	streptozotocin
SUV	standardized uptake value
SWO	segment weight optimization
TAE	transcatheter arterial embolization
TAM	tumor-associated macrophages
TAN	tumor associated neutrophils
TB	tuberculosis
TG	trialvceride
ткі	tvrosine kinase inhibitor
TNRS	trinitrobonzono sulfonio acid
	two photon avoited fluoreseense
	two-priorion excited nuorescence
	total pancreatectority and islet autotransplantation
Treg	regulatory I cells
	transient receptor potential
152	total suspended particulate

TTG	time to maximum gradient
TTP	time to peak
TUE	true unenhanced
UC	ulcerative colitis
uCd	urine cadmium
UCM	unresolved complex matter
UICC	International Union for Cancer Control
UPC	uncinate process pancreatic cancer
US	ultrasonography
USPSTF	United States Preventive Services Task Force
U-TRP2	urine trypsinogen 2
VACTERL	vertebral anomalies, anal atresia, cardiovascular anomalies,
	tracheoesophageal fistula, esophageal atresia, renal (kidney) and/or radial
	anomalies, and limb defects
VEGF	vascular endothelial growth factor
vHL	von Hippel-Lindau
VTQ	virtual touch tissue quantification
VUE	virtual unenhanced
WATSA	Whipple at the splenic artery procedure.
WHO	World Health Organization
WO	washout
WOPN	walled-off pancreatic necrosis
WOR	washout ratio
ypN	post-therapy lymph node status
урТ	post-therapy tumor stage
AJCC	American Joint Committee on Cancer
ZOL	zoledronic acid

ANATOMY AND ANOMALIES

Pancreatic volume

The purpose of one study was to estimate the volume of normal pancreas in adults using the CT volumetry (summation of the areas technique), analyze the correlation between the volume and the diameters of pancreas, which are measurable by the cross-sectional imaging, and assess the relationship with the gender, age, and body constitution. 220 CT examinations were analyzed retrospectively (102 females, 118 males; age 16-82, average 56). Following diameters were measured: cranial-caudal-CC(pancreas), CC(body&tail), CC(body), CC(head); anterior-posterior-AP(tail), AP(body), AP(head); lengths-LL(head), L(body&tail); and maximal transversal diameter of the L1 vertebral body (LL(L1)) and thickness of the abdominal subcutaneous fat (AP(ASF)), as markers of body constitution. The average volume of the pancreas was 79 ± 24 cm³ (ranging from 37 to 168 cm³). Pancreatic volume strongly correlated with all measured diameters of the pancreas. Pancreatic volume significantly correlated with gender (M:F = 86: to 73 cm³) and the LL(L1), but did not correlate with the age and the AP(ASF). Correlation of vertebral body-pancreas volume ratio of each subject and the age was strongly negative. It was concluded that marked individual variations in normal pancreas volume were observed. Pancreatic volume could be computed using the diameters measurable by the cross-sectional imaging employing a formula [001].

Different cell masses

The pancreas performs both exocrine and endocrine functions. The bulk of the pancreas is exocrine, comprising 70-90 percent acinar cells and 5-25 percent duct cells, depending on the species. Endocrine cells in the islets of Langerhans contribute only 3-5 percent of the pancreas. Pancreatic stellate cells (PSCs) comprise <5 percent of pancreas mass [002].

Patency of accessory pancreatic duct

A patent accessory pancreatic duct (APD), which acts as a safety valve, may prevent complications of endoscopic retrograde cholangiopancreatography. The interpapillary distance is probably the easiest parameter to assess the probability of APD patency. In previous studies, the patency of APD was correlated with other morphometric parameters of the accessory duct. One study assessed the frequency of APD patency among south Indian adult cadavers of both sexes, and correlated it with the interpapillary distance. Duodenopancreats specimens collected from 100 cadavers with no recorded diseases of biliary pancreatic tree were studied by routine dissection method and dye injection technique. APD had a patent communication with the duodenum in 46 specimens, and was more frequent in men. The distance between the two duodenal papillae varied from 1.6-3 cm; 98 percent of the patent APD specimens had an interpapillary distance of ≥ 2 cm. It was postulate that an duodenal interpapillary distance ≥ 2 cm suggests patency of APD [003].

Common bile duct size

The purpose of one work was to determine the size of the bile duct by echograph. The frequent injuries of the bile duct in various pathologies in particular infection, made of it a investigated organ especially by echograph. Its size can be modified by various pathologies. So it is of interest to know about its normal size. Sixty normal subjects, among which 29 women, were examined by echograph in a university hospital. They were voluntary subjects

with an empty stomach for 12 hours. Three different sonographers successively performed this examination according to the same protocol with an Aloka SSD 1700 device type and a Kontron Medical/Imagic Maestro. These devices were provided with a convex probe of 3.5megahertz multifrequency and with a linear probe of 7.5-megahertz. The subjects were in dorsal position. Reference points for the display of the bile duct were the liver, the gallbladder and the pancreas. The limits of the bile duct were marked by the cursor of the echograph. The transverse diameter (in mm) of the bile duct was measured in its origin and in its ending. No subject of the sample was obese enough to hamper the visibility of the gall-bladder and the bile duct and no subject had histories of cholecystectomy. Data analysis was made using the software Ear information version 6. Forty subjects out of 60 were between 20 and 39 years old. The transverse diameter of the bile duct was measured 38 times (63 %) in its origin and 50 times (83 %) in its ending. The failure of visibility of the proximal segment was 38 percent and the failure of visibility of the distal segment of the bile duct was 18 percent. The average transverse diameter of the bile duct in its origin was 2.6 mm; extremes were 2 and 5 mm. The average transverse diameter of the bile duct in its ending was 3.1 mm; extremes were 2 and 5 mm. The transverse diameter of the bile duct in its origin of the subjects was contained between 3 and 4 mm in 80 percent of the cases. The transverse diameter of the bile duct in its ending of the subjects was contained between 3 and 4mm in 40 percent of the cases. The difference was very significant between the diameter of the bile duct in its origin and in its ending. It was concluded that the distal segment of the bile duct was seen more accurately than the proximal segment by echograph. The diameter of the bile duct in its ending was significantly superior to that of the bile duct in its origin [004].

Arterial variability

The hepatic arterial anatomy is highly variable. A 67 year female with pancreatic mass and replaced common hepatic artery originating from the superior mesenteric artery underwent pancreaticoduodenectomy (PD). The anomalous vessel was discovered on preoperative CT scan and MRI. The vessel was dissected and preserved as it passed dorsal to the pancreas. Preservation of the blood supply to the liver and biliary tree is important after PD to prevent biliary fistula and hepatic ischaemia [005].

Celiac artery stenosis

The celiac artery arises directly from the aorta and mainly supplies blood to the liver, spleen, stomach, and duodenum. Celiac artery occlusion or stenosis was first observed in 1917, and is reportedly present in about 13-49 percent of all individuals undergoing abdominal angiography. However, it is usually of no clinical significance, because the blood supply to the upper abdominal organs is maintained through well-developed collateral pathways that develop from the superior mesenteric artery, mainly from the inferior pancreaticoduodenal artery (IPDA) to the gastroduodenal artery (GDA), through the pancreatic head area. However, in patients undergoing operative resection of the pancreatic head region, the upper abdominal organs whose blood supply originally derived from the celiac artery, such as the liver, stomach, spleen, and remnant pancreas, are at risk of necrosis from ischemia, because the resection involves these collateral vessels. Celiac axis stenosis or occlusion can be attributed to vascular causes, such as arteriosclerosis and aortitis syndrome, or nonvascular causes, such as compression by the median arcuate ligament (MAL) or nerve plexus and invasion or compression by a malignant tumor. The MAL is a connective tissue ligament that runs transversely anterior to the vertebral bodies and ventral to the abdominal aorta, and the concept of MAL compression was first described in 1963. It is believed that the celiac artery can be compressed by this ligament and narrowed at its origin, if it arises from the aorta at a higher level than normal or if the MAL exists at a lower level than normal. Compression by

the MAL is the most common cause of celiac axis stenosis, followed by arteriosclerosis, with these 2 accounting for nearly 90 percent of all the cases. A 3-dimensional CT angiograph of celiac axis stenosis caused by MAL compression is characteristic in its hooked appearance, which has traditionally been seen on lateral view aortic angiograms. In type A, intraoperative treatment is not necessary because the degree of stenosis is mild without development of collateral pathways. In type B, collateral pathways have only developed around the pancreatic head region and division of the MAL may be necessary upon resection of the pancreatic head. In type C, there is a high possibility of arterial reconstruction or preservation of the collateral pathways, which can become a large arcade from the inferior pancreaticoduodenal artery to the GDA or sometimes develop around the tail of the pancreas. During resection of the pancreatic head region, great care is exercised to preserve the collateral vessels that develop mainly from the superior mesenteric artery through the pancreatic head region, to best maintain the blood flow to the upper abdominal organs, and blood perfusion is assessed as necessary using Doppler ultrasonography. Celiac artery revascularization is considered when MAL division does not improve perfusion, when perfusion is poor after the GDA is clamped, and when there is no way to achieve GDApreserving pancreatoduodenectomy. If a direct anastomosis is not suitable or feasible, revascularization is performed using the great saphenous vein or a radial artery graft. In a preoperative assessment of celiac artery stenosis, it may be difficult to distinguish MAL compression from the other possible causes, including arteriosclerosis, in some cases. It may be important to undertake the operation being prepared for revascularization, on the assumption that division of the MAL could fail to improve the blood flow of the common hepatic artery. The methods for celiac artery revascularization include arterial anastomoses, such as middle colic artery to GDA, middle colic artery to right gastroepiploic artery, jejunal artery to GDA, and aorta to hepatic artery anastomoses, as well as bypass grafting, commonly using the great saphenous vein. Although synthetic vascular grafts are used in some cases, autologous grafts are desirable in cases undergoing surgery of the pancreatic head region, considering the potential risks of contamination during anastomosis of the gastrointestinal tract and leakage of the pancreatic fluid owing to anastomotic failure. Preoperative stenting may be an option; however, it could be fatal if thrombus formation and stent occlusion occur after invasive surgery, such as pancreatoduodenectomy, and if no other intraoperative treatment is performed. Thus, MAL division or arterial revascularization should be more reliable and secure as a first step, and it may be more advantageous to consider stenting in cases of insufficient blood perfusion after operative resection along with various procedures to encounter the MAL compression. The detailed mechanism for celiac axis stenosis caused by MAL compression is unknown, although it is considered that higher bifurcation of origin of the celiac axis or lower existence of the MAL may be possible reasons. There have been no accepted definitions of morphologic grades of celiac axis stenosis caused by MAL compression. From 1989 to 2010, 562 patients underwent operations for diseases of the pancreatic head region. To diagnose celiac artery compression by the MAL, angiography was used in the early period and 3-dimensional image reconstruction of multidetector-row computed tomography was used from 2004. The morphologic characteristics of the celiac axis stenosis were analyzed during intraoperative treatment. Twelve (2.1 %) patients were diagnosed with MAL compression, and 8 of these patients only underwent MAL division to restore the celiac artery blood flow. One patient required conservation of the collateral circulation, and 2 patients needed arterial reconstruction. In the analysis of the level of origin of the celiac axis, there were no remarkable differences between nonstenotic and stenotic cases, or between mild and severe stenotic cases. Morphologic grades were defined based on the preoperative image findings and consequent intraoperative treatments. It was concluded that preoperative grading of celiac axis stenosis could make pancreatoduodenectomy safer with maintenance of the upper abdominal organ blood flow in patients with MAL compression [006].

Lymphatic drainage

It was identified the lymphatic drainage pathways from the pancreatic head guided by indocyanine green (ICG) fluorescence imaging to analyze optimal lymphadectomy for pancreatic cancer. The lymphatic pathways in 20 patients undergoing pancreaticoduodenectomy were analyzed. It was injected ICG into the parenchyma in the anterior (n=10) or posterior surface (n=10) of the pancreas head and observed the intraoperative lymphatic flows by ICG fluorescence imaging. The seven main lymphatic drainage pathways were identified: (1) along the anterior or posterior pancreaticoduodenal arcade, (2) running obliquely down behind the superior mesenteric vein (SMV). (3) reaching the left side of the superior mesenteric artery (SMA), (4) running longitudinally upward between the SMV and SMA, (5) along the middle colic artery toward the transverse colon, (6) reaching the paraaortic (PA) region, and (7) reaching the hepatoduodenal ligament. The lymphatic pathway reaching the left side of the SMA was observed in 4 patients (20 %), while that reaching the PA region in 17 patients (85 %). The mean time to reach around the SMA was longer than that to reach the PA region. Thus it was found that several lymphatic drainage routes were observed from the pancreatic head, suggesting that a lymphadectomy around the SMA might have a similar oncological impact as that of the PA region [007].

Annular pancreas

VACTERL (V - Vertebral anomalies, A - Anal atresia, C - Cardiovascular anomalies, T - Tracheoesophageal fistula, E - Esophageal atresia, R - Renal (Kidney) and/or radial anomalies, L - Limb defects) association includes vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal dysplasia, and limb anomalies. Less frequent defects seen with VACTERL association are prenatal and postnatal growth deficiency, laryngeal stenosis, ear anomaly, large fontanels, defect of lower limb, rib anomaly, tethered cord, and defects of external genitalia. It was reported a case of VACTERL association who had concomitant biotinidase deficiency and annular pancreas, which has not been previously reported [008].

Pancreatitis, a late complication of an annular pancreas (AP), results from coexisting pancreaticobiliary malformations including pancreas divisum (PD), and pancreaticobiliary maljunction (PBM). The authors report the case of a 3-year-old boy with an unusual type of AP in which the dorsal anlage encircled the duodenum. The patient developed duodenal obstruction as well as duodenopancreatic reflux with resulting hyperamylasemia and hyperlipasemia. This type of AP associated with duodenopancreatic reflux in AP has not been reported previously. The patient was successfully treated by duodenoduodenostomy, which, by correcting the duodenopancreatic reflux, prevented the later development of pancreatitis [009].

Annular pancreas (AP) is a rare anomaly due to malrotation of the pancreatic ventral bud during embryologic development. AP has been extensively described in the pediatric population; however, in adults, the incidence has been reported to be only 1 in 22,000 patients with only a few cases presenting with simultaneous mucinous cystadenoma described in the recent literature. It was reported a case of a 72-year-old female patient with a mucinous cystadenoma, who was found to have a concomitant AP during laparoscopic distal pancreatectomy. The dual presentation of annual pancreas and mucinous cystoadenoma is an infrequent condition and can be managed with minimally invasive techniques; bypass in adults should only be performed in patients with symptomatic duodenal compression or recurrent bouts of pancreatitis [010].

Portal annular pancreas

Portal annular pancreas (PAP) is a rare variant in which the uncinate process of the pancreas extends to the dorsal surface of the pancreas body and surrounds the portal vein or superior mesenteric vein. Upon pancreaticoduodenectomy (PD), when the pancreas is cut at the neck, two cut surfaces are created. Thus, the cut surface of the pancreas becomes larger than usual and the dorsal cut surface is behind the portal vein, therefore pancreatic fistula after PD has been reported frequently. It was planned subtotal stomach-preserving PD in a 45-year-old woman with underlying insulinoma of the pancreas head. When the pancreas head was dissected, the uncinate process was extended and fused to the dorsal surface of the pancreas body. Additional resection of the pancreas body 1 cm distal to the pancreas tail to the left side of the original resection line was performed. The new cut surface complications such as pancreatic fistula occurred. Additional resection of the pancreas body may be a standardized procedure in patients with PAP in cases of pancreas cut surface reconstruction [011].

Agenesia of dorsal pancreas

Agenesis of the dorsal pancreas is an extremely rare anomaly which results from defective development of pancreas. It may be asymptomatic and incidentally detected on cross sectional imaging. Till now less than 100 cases of dorsal agenesis of pancreas have been reported in the world literature. The dorsal pancreatic agenesis is described in two forms, the partial and the complete form. The pancreas is formed by ventral and dorsal endodermal buds. The dorsal bud forms the upper part of the head, body and tail of the pancreas and drains through the duct of Santorini. The ventral bud gives rise to the major part of the head and uncinate process which drains through the duct of Wirsung. At 6-7 weeks of gestation the fusion between ventral and dorsal pancreas occurs. During the complex development, congenital abnormalities can occur. Complete agenesis of the pancreas and agenesis of the ventral pancreas are not compatible with life. Agenesis of the dorsal pancreas is described in two forms; partial or complete. In complete dorsal agenesis, the minor papilla, accessory pancreatic duct, body and tail of the pancreas are absent. In partial agenesis, the minor papilla with a remnant of the accessory pancreatic duct and the neck and proximal body of pancreas are present. In dorsal pancreatic agenesis, the body and tail are absent and the pancreatic bed anterior to splenic vein is filled with stomach and bowel loops described as dependent stomach and dependent intestine sign on CT. The stomach and intestinal loops when air filled appear as an echogenic structure in the pancreatic bed that may interfere with adequate visualization of body and tail of pancreas, on ultrasonography examination. This may be misinterpreted as normal body and tail of pancreas on ultrasound examination by inexperienced examiner. When ultrasonography examination is suboptimal, we have found that the adequately distended fluid filled stomach following water ingestion provides a good window for proper visualization of the pancreatic body and tail. CT and MRI studies are useful for evaluating pancreatic body and tail when above method fails. T2 weighted sequence on MRI is better than T1 weighted fat saturated spoiled gradient sequence for depicting presence of bowel loops in pancreatic bed. In the later sequence, the collapsed small bowel loops in the distal pancreatic bed appear isointense with the pancreatic head and may be misinterpreted as normal pancreatic body and tail in absence of any intervening gap between them. Distal pancreatic lipomatosis and pseudoagenesis must be considered in the differential diagnosis of dorsal agenesis. Atrophy of the body and the tail of pancreas secondary to acute or chronic pancreatitis, with sparing of the uncinate process may mimic dorsal pancreatic agenesis and has been labeled as pseudoagenesis of the pancreas. This can be differentiated by demonstrating dorsal duct which is either absent or very short in dorsal agenesis and it is usually present in lipomatosis and pseudoagenesis. These findings

along with dependent stomach and/or dependent intestine signs on multidetector CT can allow differentiation of the agenesis of dorsal pancreas from distal lipomatosis obviating invasive procedure like angiography. However, the diagnosis of agenesis of the dorsal pancreas is inconclusive without demonstration of the absence of dorsal pancreatic duct, either with endoscopic retrograde pancreatography or MRCP. Patients with this anomaly may be asymptomatic or may present with diabetes mellitus, epigastric pain, acute or chronic pancreatitis. It was reported the computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) findings in three cases with dorsal pancreatic agenesis, one with partial and the other two with complete form. Speckled calcification at pancreatic head was observed in one patient. Lateral contour lobulation of pancreatic head which is seen in one third of normal population is believed to be due to variation in fusion between ventral and dorsal pancreas. In contrast, we observed lateral contour lobulation of pancreatic head in a case of complete agenesis of the dorsal pancreas where structures derived from dorsal pancreas are undeveloped. The ventral and dorsal pancreatic duct lengths were measured on MRCP images and we observed that in partial agenesis, the duct of Wirsung was shorter in length, compared to the duct of Santorini. The duct of Wirsung was relatively longer in cases of complete agenesis of the dorsal pancreas. It was concluded that the CT, MRI and MRCP findings in dorsal pancreatic agenesis and the relationship between the length of ventral duct with the type of dorsal pancreatic agenesis will provide a new insight into this particular anomaly [012].

Dorsal agenesis of the pancreas is a rare congenital disorder. It was reported a case of a 65year-old man with mild abdominal pain and insulin-dependent diabetes mellitus. Computed tomography (CT) of the abdomen showed a short pancreas with no pancreatic tissue ventral to the splenic vein. Magnetic resonance cholangiopancreatography (MRCP) visualized the absence of a dorsal duct system and confirmed the suspicion of complete agenesis of the dorsal pancreas. Endoscopic ultrasound (EUS) was also performed to rule out pancreatic malignancy [013].

Heterotopic pancreas

In the gall-bladder

It was reported an associating heterotopic pancreas in the gallbladder and elevated pancreatic enzymes in bile. A 60-year-old woman underwent abdominal ultrasonography at a medical check-up, revealing a nodular protrusion at the neck of the gallbladder. It seemed likely to be a lymph node, but we could not exclude the possibility of gallbladder cancer. In order to make a correct diagnosis, laparoscopic cholecystectomy was successfully performed. Pathological examination revealed heterotopic pancreatic tissue in the gallbladder wall. In addition, it was detected elevated levels of amylase and lipase in gallbladder bile. Preoperative diagnosis of heterotopic pancreas in the gallbladder is difficult. However, an increase of pancreatic enzymes in gallbladder bile may potentially play an important role in the occurrence of acalculous cholecystitis and biliary cancer [014].

There was also another report ectopic pancreas in the gallbladder [015].

In esophagus

It was reported a case of a 58-year-old woman presenting with dysphagia secondary to an intraductal papillary mucinous neoplasm arising from a heterotopic pancreas in the oesophageal wall. This was successfully treated with a laparoscopic/thoracoscopic ivor Lewis oesophagectomy. Dysphagia is the most common symptom of oesophageal tumours regardless of aetiology of the tumour and can be treated successfully with surgical resection.

Through an extensive search of the literature, it was found that a heterotopic pancreas in the oesophagus is extremely rare with only ten cases being reported. It was described what we believe to be the first case of a heterotopic pancreas in the oesophagus transforming into an intraductal papillary mucinous neoplasm [016].

Duodenal obstruction

A 9-year-old boy presented with duodenal pancreatic rest causing obstruction and required surgical intervention. He had been treated at the age of 4 months for a choledochal cyst. Both choledochal cyst and heterotopic pancreas are entities that are commonly encountered in children, but the incidental presence of both the entities in the same child, albeit presenting metachronously, is extremely rare [017].

In jejunum

Acute pancreatitis occurring in an aberrant pancreas (acute aberrant pancreatitis) is a rare clinical condition. A 67-year-old male was referred to the emergency department complaining of severe epigastralgia. He was evaluated by computed tomography, and the findings suggested jejunal penetration into the mesentery and abscess formation. It was performed emergency surgery and found a mass located in the jejunal mesentery. Intraoperatively, we diagnosed it to be a malignant tumor complicated by penetration, and it was performed a partial resection of the jejunum to remove the mass. Based on the pathological results, it was evident that this was a case of acute aberrant pancreatitis occurring on a background of chronic pancreatitis. The patient had an uneventful postoperative course. This report is the first presentation describing the possible mechanism that contributes to the process of infected pancreatic necrosis in an aberrant pancreas [018].

In mediastinum

In a mediastinal cyst

Heterotopia of pancreatic tissue is a common developmental anomaly. Although ectopic pancreatic tissue is mostly found in the gastrointestinal tract, localization in the mediastinum is extremely rare. It was reported a 32-year-old male patient who had an urgent thoracotomy two years ago due to a thoracic surgery. During the thoracotomy fragments of a partly necrotic cystic mass in the right thorax were removed and decortication was performed. Two years later the patient was hospitalized again because of haemoptoe and atypical chest pain. A residual cystic mass was detected between the right hilum and the ascending aorta connecting to the pericardium, the superior vena cava and the aorta on the chest CT. After the operation a mediastinal cyst was diagnosed, with a pancreatic tissue by histology [019].

Anomalous union of the pancreatico-biliary duct

To demonstrate the imaging findings of biliopancreatic and pancreatico-biliary reflux in patients with anomalous union of the pancreatico-biliary duct (AUPBD) on gadoxetic acidenhanced functional magnetic resonance cholangiography (fMRC) a study included six consecutive patients (two men and four women; mean age 48 years) with AUPBD. All subjects underwent endoscopic retrograde cholangiopancreatography (ERCP); one subject also underwent bile sampling of the common bile duct (CBD) to measure the amylase level because his gadoxetic acid-enhanced fMRC images showed evidence of pancreatico-biliary reflux of pancreatic secretions. Of the five patients with choledochal cysts, four underwent pylorus-preserving pancreaticoduodenectomy. The five cases of choledochal cysts were classified as Todani classification I. In three of the six patients with AUPBD, injected contrast media reached the distal CBD and pancreatic duct on delay images, suggesting biliopancreatic reflux. In two of these six patients, a band-like filling defect was noted in the CBD on pre-fatty meal images, which decreased in size on delayed post-fatty meal images, suggesting pancreatico-biliary reflux of pancreatic secretions, and the bile sampled from the CBD in one patient had an amylase level of 113,000 IU/L. In one of the six patients with AUPBD, contrast media did not reach the distal CBD due to multiple CBD stones. It was concluded that gadoxetic acid-enhanced fMRC successfully demonstrated biliopancreatic reflux of bile and pancreatico-biliary reflux of pancreatic secretions in patients with AUPBD with and without choledochal cysts [020].

Intrapancreatic accessory spleen (splenunculus)

Intrapancreatic accessory spleen is not an uncommon entity and usually located in the tail of the pancreas. Most of them are asymptomatic and incidental findings on radiologic study or at autopsy. On imaging study, it appears to be a well-defined, solitary, and hypervascular lesion; therefore, it may be confused with pancreatic neoplasms, such as neuroendocrine neoplasm, well-differentiated adenocarcinoma, solid pseudopapillary tumor, or metastatic tumor to the pancreas. As such, the diagnostic fine-needle aspiration biopsy of the lesion may be performed. Several case reports describing cytological features of the lesion have been published in recent years. Among them, the most commonly identified cytological findings are sheets of a heterogeneous population of lymphocytes and prominent traversing blood vessels. Herein, we report an unusual EUS-FNA case of intrapancreatic accessory spleen. In addition to above previously well-described cytological features, one case revealed many cells with fine granular chromatin and areas with pseudo rosette-like architecture, mimicking and engendering the differential diagnosis of pancreatic neuroendocrine tumors [021].

A case of accessory spleen located in the tail of the pancreas in a stillbirth male foetus is reported. The congenital anomaly was revealed at autopsy. The intrapancreatic spleen was well demarcated and was composed of red and white pulp; however, same pancreatic ducts were intermingled with the splenic parenchyma. As well as the intrapancreatic lesion another minute accessory spleen was also found at the hilum of the proper organ. Since a lack of morphological features of trisomy 13 syndrome were found in the foetus, the ectopic spleens were regarded as incidental findings [022].

Intrapancreatic accessory spleen (IPAS) is a rare benign lesion of the pancreas that frequently clinically and radiographically mimics a solid neoplasm. Very rarely, epidermoid cysts may form in IPAS and be mistaken for a cystic neoplasm of the pancreas on radiographic imaging. IPAS and epidermoid cyst involving intrapancreatic cyst (ECIPAS) are benign, and, if recognized, do not require surgical intervention. There are few reports of the cytopathologic features of IPAS diagnosed by fine needle aspiration (FNA). It was reported a series of 6 cases of endoscopic ultrasound (EUS)-guided FNA of IPAS, 3 of which had histological confirmation, including 1 case of histologically confirmed ECIPAS. Cytomorphologic features of IPAS include a polymorphous population of hematopoietic cells, including lymphocytes, eosinophils, histiocytes, plasma cells, and red blood cells, admixed with numerous small blood vessels representing splenic sinusoids. CD8 immunostaining of cell block or core biopsy material highlights splenic endothelial cells and confirms the diagnosis. FNA of ECIPAS reveals predominantly macrophages and proteinaceous debris. Diagnostic pitfalls include pancreatic neuroendocrine tumor. If IPAS is recognized as a diagnostic consideration on EUS-FNA, unnecessary surgical resection may be avoided [023].

Epithelial inclusion cyst arising within an intra-pancreatic splenunculus

An accessory spleen (splenunculus) may occur in up to 10 percent of the general population. However, an epithelial inclusion cyst originating within an intra-pancreatic splenunculus is an extremely rare finding, with only twenty-two previous cases described in medical literature. A 51-year-old male presented to our institution for investigation of altered bowel habit. Endoscopic ultrasound examination and CT scanning demonstrated an 18 mm cystic, well-demarcated lesion in the tail of the pancreas, resembling malignancy. Following laparoscopic spleen-preserving distal pancreatectomy, histological analysis confirmed epithelial inclusion cyst arising within an intra-pancreatic splenunculus. The pre-operative radiological identification of such cystic pancreatic lesions is challenging. Surgical resection is usually performed for clinical suspicion of pancreatic malignancy [024].

PHYSIOLOGY

Purinergic signaling

Pancreatic cells contain specialised stores for ATP. ATP was shown to be released together with insulin from pancreatic secretary granules by exocytosis in 1975, similar to the release of ATP with noradrenaline (NA) from adrenal chromaffin granules [Leitner et al, 1975]. ATP was shown to stimulate glucagon and insulin secretion from isolated perfused rat pancreas in 1976, and this was dependent on low and high glucose concentrations respectively [Loubatières-Mariani et al, 1976]. The ATP released from secretary granules was shown to be broken down to ADP and AMP [Sussman & Leitner, 1977] and ecto-ATPases were identified [Levin et al, 1978]. Adenosine, also resulting from ATP breakdown, inhibited insulin secretion stimulated by glucose [Ismail et al. 1977]. On the other hand, adenosine, ADP and 5'-AMP released glucagon in isolated perfused rat pancreas [Weir et al, 1975]. It was shown that the relative potency of nucleotides that increased insulin release induced by glucose was ATP \geq ADP, while AMP and adenosine had only weak activity (about 100-fold less active) and GTP, ITP, CTP and UTP were virtually inactive [Loubatières-Mariani et al, 1979]. Almost 50 years ago, the first reports on the role of purinergic signalling in the endocrine pancreas appeared. Stimulation of secretion of insulin by ATP was first reported in 1963 for rabbit pancreas slices [Rodrigue-Candela et al, 1963] and confirmed later in primates [Levine et al, 1970]. Purinergic receptors (P2 and P1) and ecto-nucleotidases are expressed in both endocrine and exocrine calls, as well as in stromal cells. The pancreas, especially the endocrine cells, is an early target for the actions of ATP. After the historical perspective of purinergic signalling in the pancreas, the focus of this review will be the physiological functions of purinergic signalling in the regulation of both endocrine and exocrine pancreas. Next, we will consider possible interaction between purinergic signalling and other regulatory systems and their relation to nutrient homeostasis and cell survival. The pancreas is an organ exhibiting several serious diseases - cystic fibrosis, pancreatitis, pancreatic cancer and diabetes - and some are associated with changes in life-style and are increasing in incidence. There is upcoming evidence for the role of purinergic signalling in the pathophysiology of the pancreas, and the new challenge is to understand how it is integrated with other pathological processes [002].

Neural regulation of the pancreas

The activities of both endocrine and exocrine cells are regulated by parasympathetic and sympathetic nerves, as well as by hormones, autocrine and paracrine mediators. Intrapancreatic parasympathetic nerves are present at day 14 of gestation in the foetal rat pancreas, but no sympathetic innervation was detected at that stage. ATP and acetylcholine (ACh) have synergistic effects on insulin release, consistent with their roles as cotransmitters from parasympathetic nerves. Parasympathetic stimulation can evoke secretion from both exocrine acini and ducts. In addition, ACh and ATP also have synergistic effects on exocrine secretion, though it may involve separate neural and exocrine components. Effector cells are considered to be innervated when they form close relationships with axonal varicosities and such relationships have been shown between sympathetic nerve varicosities and both alpha- and delta-cells, but less so with beta-cells. Sympathetic nerve stimulation inhibits insulin secretion, perhaps via the alpha_{2A}-receptor-mediated opening of ATPdependent K⁺ channels. Sympathetic nerve stimulation directly regulates exocrine ducts and acinar cells via beta-adrenergic receptors though the major effect is on blood vessels where it would cause vasoconstriction. In addition, sympathetic nerves (probably releasing NA and ATP as co-transmitters) indirectly regulate pancreatic endocrine and exocrine secretions, through actions on the parasympathetic ganglia in the pancreas [002].

Pancreatic vasculature

Some of the earliest experiments on ATP-induced insulin release were carried out on isolated perfused pancreas. Apart from reaching islet cells, ATP could also have an effect on vasculature. Evidence for the presence of P2 receptors on vascular smooth muscle in rat pancreas was presented in earlier studies. P2X receptors mediate vasoconstriction of the rat pancreatic vascular bed, while P2Y receptors mediate vasodilation probably via endothelial-derived relaxing factor affecting smooth muscle cells. Adenosine receptors, probably A_{2A}, mediate vasorelaxation in the pancreatic vascular bed. Adenosine may be protective in pancreatitis and as indicated by the following experiments. Infusion of homocysteine, a risk factor for atherosclerosis, altered cholinergic endothelium-mediated vasodilation, but did not affect adenosine-mediated endothelial-independent dilation of vascular smooth muscle [002].

Ecto-nucleotidases

There are several types of nucleotide- and side-modifying enzymes expressed in various pancreatic cells. Biochemical studies have shown membrane Mg²⁺- or Ca²⁺-activated adenosine triphosphatase activities in rat pancreas. Later, ATP diphosphohydrolase was identified in pig pancreas hydrolysing ATP to ADP and AMP. Eventually, in 1995, it was possible to purify and identify type-1 ecto-nucleoside triphosphate diphosphohydrolase (denoted NTPDase or CD39 family) in pig pancreas. One study on rat pancreas showed ATPase, ADPase, 5'-nucleotidase and alkaline phosphatase activity in the vasculature. endocrine and exocrine cells. Similar studies at that time show that ATP/ADPase activity was strongest in vasculature, ATPase was detected in both endocrine and exocrine cells, while endocrine but not exocrine cells contained alkaline phosphatase. In endocrine pancreas, ATP pyrophosphohydrolase (ecto-NPP) and alkaline phosphatase were shown in isolated mouse pancreatic islets. A monoclonal antibody has been prepared as a specific inhibitor of human NTPDase-3, which is expressed in all Langerhans islet cells. Regarding exocrine pancreas, based on functional and expression studies, it was found that the rat pancreas contains NTPDase-1 in acinar granules and ducts. Upon stimulation, the enzyme is secreted in particular form (microvesicles) to pancreatic juice. Indeed, presence of NTPDase-1 in zymogen granules, first detected biochemically was confirmed by proteomics and western blot analysis. Further immunohistochemical studies have shown that NTPDase-1 and -2 (CD39L1) were also localised in mouse pancreas (Kittel et al. 2004). Acinar cells were positive for both NTPDase-1 and -2, but their expression in ductal epithelial cells was weak. In addition, NPTDase-1 was found in blood vessels and NTPDase-2 immunostaining in the basolateral aspect of endothelial cells. In agreement with the above studies, ecto-ATPase activity was demonstrated by enzyme histochemistry in both pancreatic acini and ducts in rats, but it was not detected in guinea pigs and humans, perhaps indicating species differences in purinergic regulation of pancreatic secretion, or limitations of the detection technique. Cholecystokinin octapeptide (CCK-8) stimulation of the pancreas causes release of both ATP-consuming enzymes (NTPDase-1 and 5'-nucleotidase, i.e. CD39 and CD73) and ATP-generating enzymes (adenylate kinase and nucleoside diphosphate kinase) into pancreatic juice. These studies support the idea that intraluminal ATP/adenosine concentrations are regulated within the pancreatic ductal tree and serve to stimulate ductal P2 and adenosine receptors [002].

Pancreatic acini

Acinar cells secrete fluid containing NaCl and a variety of digestive enzymes, including alpha-amylase, lipase, colipase, carboxylester lipase, zymogens such as trypsinogen, chymotrypsinogen, procarboxypeptidases, and proelastase as well as trypsin inhibitor pancreatitis-associated protein and lithostathine. This enzyme-rich secretion passes through a series of ducts that secrete a NaHCO₃-rich fluid to the duodenum, where together with bile and duodenal secretions it acts on materials entering the duodenum. Pancreatic acini

release ATP in response to various stimuli, including cholinergic and CCK-8 stimulation. A paper showed that ATP accumulates in zymogen granules due to the action of vesicular nucleotide transporter, which belongs to the SLC17A9 solute family and is expressed in the brain and adrenal chromaffin cells. Although pancreatic acini store and release ATP from granules, acini are relatively unaffected by ATP, possessing relatively few functional P2 receptors; the main site of ATP effects are the downstream ducts. Thus only about 15 percent of acinar cells in adult rat pancreas respond to UTP and ATP, although transcripts for P2Y₂, P2Y₄, P2X₁ and P2X₄ receptors were present. The authors speculated that the low number of functional P2 receptors in acini might be related to the fact that these cells release ATP and autocrine stimulation should be avoided. A recent study on mouse pancreas pieces confirms very low functionality of P2 receptors in acinar cells compared to surrounding PSC. ATP released from acini, hydrolysed to adenosine, could stimulate duct or acinar cells. There are several types of adenosine receptors expressed in whole pancreas. It has been known for a long time that adenosine has multiple effects on exocrine pancreas. Adenosine increased amylase secretion in rat pancreatic lobules, but since the effect was inhibited by atropine and could not be reproduced in isolated acini, it was concluded that the adenosine effect was mediated indirectly by release of neural Ach [002].

Pancreatic ducts

The principal physiological role of pancreatic ducts is to secrete a bicarbonate-rich isotonic fluid. This is achieved by coordinated action of several H⁺/HCO₃⁻ transporters, cAMP- and/or Ca²⁺-activated Cl⁻ channels and K⁺ channels. In contrast to acini, pancreatic duct cells respond very well to ATP and UTP. Early studies show that ATP and UTP applied to the basolateral surface of rat pancreatic duct cells increased [Ca²⁺] and transiently stimulated K⁺ and Cl⁻ conductances. ATP and UTP also activated large Ca²⁺-dependent Cl⁻ currents, and smaller K⁺ currents, in CAPAN-1 and CFPAC-1 cells, human pancreatic duct cell lines. Also in dog pancreatic duct epithelial cells, ATP and UTP stimulated Ca²⁺-activated Cl⁻ and K⁺ conductances, again most likely via P2Y₂ receptors. RT-PCR and functional studies showed that pancreatic ducts express P2Y₂, P2Y₄, P2X₁, P2X₄, P2X₇ and probably other P2 receptors such as P2Y₁ and P2Y₁₁. As in other epithelia, P2 receptor localisation is difficult to reveal, as the same receptor type can be localised to both luminal and basolateral membranes, though coupled to different ion transporters. Thus luminal ATP/UTP, most likely via P2Y₂ receptors, stimulates fluid and Cl⁻/HCO₃⁻ secretion. P2X₇ receptors, most likely luminal, are cation channels but also decrease intracellular pH, possibly reflecting HCO₃ secretion. A recent study shows that P2X₇ receptors act in conjunction with muscarinic receptors to increase exocrine secretion in pancreas and this secretion was reduced in P2X₇ KO mice. P2 receptors can also down-regulate secretion, e.g. basolateral P2Y₂ receptors inhibit K⁺ channels (KCNMA1, K_{ca}1.1) and thereby ductal secretion. In addition to HCO₃⁻ and fluid secretion, larger pancreatic ducts in particular also secrete mucins as demonstrated in dog pancreatic duct epithelial cells. P2Y₂ receptors stimulated exocytosis detected by microamperometry and cAMP greatly potentiated the Ca2+-mediated effects. RT-PCR and immunohistochemical studies of human pancreatic duct cell lines, PANC-1 and CFPAC-1, demonstrated later the presence of P2Y₁, P2Y₂, P2Y₄, P2Y₆, P2Y₁₁₋₁₄ and P2X₁, P2X₂, P2X₄, P2X₅, P2X₆ and P2X₇ receptors and some were also found in another cell line CAPAN-1. Purinergic receptors mediate Na⁺/Ca²⁺ exchange in pancreatic duct cells and it is proposed that this plays a role in the regulation of duct lumen Ca²⁺ content. Pancreatic ducts, both human and rodent, also express functional adenosine receptors, primarily of the A_{2A} and A_{2B} subtypes, stimulation of which results in the opening of Cl⁻ channels that are required for HCO₃ and fluid secretion. This finding supports nicely earlier studies performed on dog whole pancreas. Although adenosine decreased blood flow, it enhanced secretin-stimulated HCO₃ and fluid secretion. A pharmacological study indicated that it was the A_{2A} adenosine receptor that was involved in this secretory response in dog pancreas. Acini secrete ATP and ecto-nucleotidases, and ATP and adenosine (not ADP) are agonists for pancreatic ducts, helping to regulate ion transport and thereby secretion. Neural and mechanically released
ATP may also be stimulatory, but possibly at large concentrations it may be inhibitory and down-regulate secretion in order to prevent over-stimulation and distension of ducts. In the case of acinar damage significant amounts of ATP could be released towards the interstitium. At this stage one can only speculate how this might affect endocrine cells, immunoreactive cells, sensory nerves, as well as PSCs [002].

Pancreatic stellate cells

PSCs are relatively newly discovered cells that play crucial roles in pancreatic inflammation and fibrosis; in addition, it is reputed that they have the potential to become insulin-producing cells. Purinergic signalling has not been extensively investigated yet. First reports show that especially activated PSC respond with increases in $[Ca^{2+}]_i$ to micromolar concentrations of ATP. Several types of P2Y and P2X receptors are expressed in these cells, mRNA for P2Y₁, P2Y₂, P2Y₆, P2X₁, P2X₄, P2X₅ but not P2X₇ was detected, though another study indicates also mRNA for the P2X₇ receptor. Robust $[Ca^{2+}]_i$ responses to ATP, UTP and UDP and relative insensitivity to extracellular Ca^{2+} indicate strong responses from the P2Y₂ and P2Y₆ receptors. ATP, as well as protease-activated receptors (PAR1 and -2) and platelet-derived growth factor, also results in prominent nuclear Ca^{2+} signals, which may play a role in PSC proliferation and contributes to the development of pancreatic diseases [002].

Bicarbonate

Fluid and HCO₃⁻ secretion is a vital function of all epithelia and is required for the survival of the tissue. Aberrant fluid and HCO₃ secretion is associated with many epithelial diseases, such as cystic fibrosis, pancreatitis, Sjögren's syndrome, and other epithelial inflammatory and autoimmune diseases. Significant progress has been made over the last 20 years in our understanding of epithelial fluid and HCO₃ secretion, in particular by secretory glands. Fluid and HCO₃ secretion by secretory glands is a two-step process. Acinar cells secrete isotonic fluid in which the major salt is NaCl. Subsequently, the duct modifies the volume and electrolyte composition of the fluid to absorb the Cl⁻ and secrete HCO₃⁻. The relative volume secreted by acinar and duct cells and modification of electrolyte composition of the secreted fluids varies among secretory glands to meet their physiological functions. In the pancreas, acinar cells secrete a small amount of NaCI-rich fluid, while the duct absorbs the CI⁻ and secretes HCO₃ and the bulk of the fluid in the pancreatic juice. Fluid secretion appears to be driven by active HCO(3)(-) secretion. In the salivary glands, acinar cells secrete the bulk of the fluid in the saliva that is driven by active Cl⁻ secretion and contains high concentrations of Na⁺ and Cl⁻. The salivary glands duct absorbs both the Na⁺ and Cl⁻ and secretes K⁺ and HCO_3 . In one review, it was focueds on the molecular mechanism of fluid and HCO_3 . secretion by the pancreas and salivary glands, to highlight the similarities of the fundamental mechanisms of acinar and duct cell functions, and to point out the differences to meet glandspecific secretions [025].

Pancreatic juice secretion

Apelin

Apelin is known to stimulate cholecystokinin (CCK) and inhibit insulin release, however the mechanisms on pancreatic secretion remain unclear. The present study aimed to determine the expression of apelin and apelin receptor in the pancreas by immunofluorescence studies and the effect of exogenous apelin on the secretion of pancreatic juice in anesthetized rats. Pancreatic-biliary juice (P-BJ) was collected from Wistar rats treated with apelin (10, 20 and 50 nmol/kg b.w., boluses given every 30 min intravenously or intraduodenaly). The same

apelin doses were administered to rats subjected to intraduodenal tarazapide, capsaicin or vagotomy. Pancreatic blood flow was measured by a laser doppler flowmeter. Direct effects of apelin were tested on dispersed acinar cells. Apelin receptor was expressed on acinar cells, pancreatic duct and islets cells, whereas apelin in pancreatic acini, but not in the islets. Intravenous apelin decreased P-BJ volume, protein and trypsin outputs in a dose-dependent manner. In contrast, intraduodenal apelin stimulated P-BJ secretion. Pharmacological block of mucosal CCK1 receptor by tarazepide, vagotomy and capsaicin pretreatment abolished the effects of intravenous and intraduodenal apelin on P-BJ volume, protein and trypsin outputs. Apelin decreased the pancreatic blood flow. Apelin at 10⁻⁶ M increased the release of amylase from non-stimulated and CCK-8-stimulated acinar cells. In conclusion, apelin can affect the exocrine pancreas through a complex mechanism involving local blood flow regulation and is driven by vagal nerves [026].

Insulin protection of pancreatic acinar cells

Acute pancreatitis is a serious and sometimes fatal inflammatory disease of the pancreas without any reliable treatment or imminent cure. In recent years, impaired metabolism and cytosolic Ca^{2+} ([Ca^{2+})])_i overload in pancreatic acinar cells have been implicated as the cardinal pathological events common to most forms of pancreatitis, regardless of the precise causative factor. Therefore, restoration of metabolism and protection against cytosolic Ca²⁺ overload likely represent key therapeutic untapped strategies for the treatment of this disease. The plasma membrane Ca2+-ATPase (PMCA) provides a final common path for cells to "defend" [Ca²⁺], during cellular injury. In one paper, it was used fluorescence imaging to show for the first time that insulin treatment, which is protective in animal models and clinical studies of human pancreatitis, directly protects pancreatic acinar cells from oxidantinduced cytosolic Ca²⁺ overload and inhibition of the PMCA. This protection was independent of oxidative stress or mitochondrial membrane potential but appeared to involve the activation of Akt and an acute metabolic switch from mitochondrial to predominantly glycolytic metabolism. This switch to glycolysis appeared to be sufficient to maintain cellular ATP and thus PMCA activity, thereby preventing Ca²⁺ overload, even in the face of impaired mitochondrial function [027].

Pancreatic pain

Pain management of many pancreatic diseases remains a major clinical concern. This problem reflects our poor understanding of pain signaling from the pancreas. One review provided an overview of the current knowledge, with emphasis on current pain management strategies and recent experimental findings. A systematic search of the scientific literature was carried out using EMBASE, PubMed/MEDLINE, and the Cochrane Central Register of Controlled Trials for the years 1965-2011 to obtain access to all publications, especially randomized controlled trials, systematic reviews, and meta-analyses exploring pain and its management in disease states such as acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC). Over the last decade, numerous molecular mediators such as nerve growth factor and the transient receptor potential (TRP) cation channel family have been implicated in afferent nerve signaling. More recent animal studies have indicated the location of the receptive fields for the afferent nerves in the pancreas and shown that these are activated by agents including cholecystokinin octapeptide, 5-hydroxytryptamine and bradykinin. Studies with PC specimens have shown that neuro-immune interactions occur and numerous agents including TRP cation channel V1, artemin and fractalkine have been implicated. Experimental studies in the clinical setting have demonstrated impairment of inhibitory pain modulation from supraspinal structures and implicated neuropathic pain mechanisms. It was concluded that our knowledge in this area remains incomplete.

Characterization of the mediators and receptors/ion channels on the sensory nerve terminals are required in order to facilitate the development of new pharmaceutical treatments for AP and CP [028].

DIABETES

Hyperinsulinemia

One model proposes that environmentally induced elevated background levels of insulin, superimposed on a susceptible genetic background, or basal hyperinsulinemia is the root cause of insulin resistance, obesity, and diabetes. There is a strong relationship between basal insulin levels, obesity, and diabetes in humans. Increasing fasting insulin levels compared with those in lean control subjects have been documented as subjects progress from obesity to impaired glucose tolerance and severe diabetes. This correlation provides no information on causation, and the same relationship with insulin resistance could be shown. However, there is evidence that hypersecretion of insulin can precede and cause insulin resistance. For example, rodents infused with insulin via an implanted minipump become hyperinsulinemic and insulin resistant with impaired glucose tolerance. Furthermore, in human studies, inhibition of hyperinsulinemia with diazoxide actually causes weight loss and decreases insulin levels without impairing glucose tolerance in obese humans. These studies suggest that hyperinsulinemia can cause insulin resistance and that lowering insulin secretion in hyperinsulinemic individuals may be beneficial. A fictitious factor X may influence insulin secretion by acting directly on the beta-cell or indirectly by changing the circulating redox indicators produced through an effect on another organ. If an increase in insulin secretion is sustained, an increase in insulin-generated signals throughout the body occurs. This can cause hepatic insulin resistance and increased fat mass - both key pathophysiological components of obesity and type 2 diabetes. In this conceptual model, insulin resistance is caused by hyperinsulinemia and is an appropriate adaptation to the increased need to store fat in adipose tissue without causing hypoglycemia. Thus, insulin resistance is an adaptive response that successfully maintains normal circulating levels of fat and glucose as long as the beta-cell is able to maintain sufficiently elevated insulin levels. Perhaps the time has come to expand our research focus to carefully investigate the environmental changes that have accompanied the epidemic of obesity and diabetes [029].

Glucagon

Pancreatic islet alpha-cell glucagon secretion is critically dependent on pancreatic islet betacell insulin secretion. Normally, a decrease in the plasma glucose concentration causes a decrease in beta-cell insulin secretion that signals an increase in alpha-cell glucagon secretion during hypoglycemia. In contrast, an increase in the plasma glucose concentration, among other stimuli, causes an increase in beta-cell insulin secretion that signals a decrease, or at least no change, in alpha-cell glucagon secretion after a meal. In absolute endogenous insulin deficiency (i.e. in type 1 diabetes and in advanced type 2 diabetes), however, beta-cell failure results in no decrease in beta-cell insulin secretion and thus no increase in α -cell glucagon secretion during hypoglycemia and no increase in beta-cell insulin secretion and thus an increase in alpha-cell glucagon secretion after a meal. In type 1 diabetes and advanced type 2 diabetes, the absence of an increment in glucagon secretion, in the setting of an absent decrement in insulin secretion and an attenuated increment in sympathoadrenal activity, in response to falling plasma glucose concentrations plays a key role in the pathogenesis of iatrogenic hypoglycemia. In addition, there is increasing evidence that, in the aggregate, suggests that relative hyperglucagonemia, in the setting of deficient insulin secretion, plays a role in the pathogenesis of hyperglycemia in diabetes. If so, abnormal glucagon secretion is involved in the pathogenesis of both hypoglycemia and hyperglycemia in diabetes [030].

ENDOSCOPY

A protocol for biliary cannulation

Traditionally, a 2-step protocol has been used for deep biliary cannulation. The purpose of one prospective study was to find out the feasibility and safety of the novel sequential 3-step protocol (traditional cannula with guidewire, double-guidewire, and needle-knife techniques) for deep biliary cannulation. All consecutive patients admitted for endoscopic retrograde cholangiopancreatography (ERCP) to a single, very experienced ERCP endoscopist during the year 2009 with intended biliary cannulation and with unhindered access to a native papilla (n=105) were included in the present study. The overall success rate for deep biliary cannulation was 99% (104/105). Cannulation with cannula and guidewire was attempted in all patients and proved successful in 80 percent (84/105) of the attempts, the doubleguidewire technique was applied in 19 percent (20/105) and was successful in 65 percent (13/20) of the cases, and the needle-knife technique was applied in 7% (7/105) with success in all cases. The median cannulation time was 1 minute (range, 0 to 27 min). The rate of post-ERCP pancreatitis was 3 percent (3/105) and post-ERCP cholangitis 2 percent (2/105). It was concluded that in experienced hands, the novel sequential 3-step protocol for biliary cannulation tested herein proved to be an effective cannulation protocol with the overall success rate of 99 percent. The complication rate of these ERCP procedures (5 %) was within acceptable limits [031].

ERCP-related duodenal perforations

Management of endoscopic retrograde cholangiopancreatography (ERCP)-associated duodenal perforation remains controversial. Some recommend surgery, while others recommend conservative treatment. A retrospective chart review was conducted to identify patients treated at one institution for ERCP-related duodenal perforations. Study variables included indication for ERCP, clinical presentation, diagnostic procedures, time to diagnosis and treatment, location of injury, management, length of stay in hospital and survival. Between 2000 and 2009, 12 232 ERCP procedures were performed at one centre, and perforation occured in 11 patients (0.08 %; 5 men, 6 women, mean age 71 years). Six of the perforations were discovered during ERCP; 5 required radiologic imaging for diagnosis. Three perforations were diagnosed incidentally by follow-up ERCP. In 1 patient, perforation occurred 3 years after the procedure owing to a dislocated stent. Four of 11 perforations were stent-related; in 2 patients ERCP was performed in a nonanatomic situation (Billroth II gastroenterostomy). Free peritoneal perforation occurred in 4 patients; 1 was successfully managed conservatively. Four patients (36 %) were treated surgically and none died. Five patients were managed conservatively with a successful outcome, and 2 patients died after conservative treatment (18%). Operative treatment included hepaticojejunostomy and duodenostomy (1 patient), suture of the perforation with T-drain (1 patient) and suture only (2 patients). The mean length of stay in hospital for all patients was 20 days. It was concluded that post-ERCP duodenal perforations are associated with significant morbidity and mortality. Immediate surgical evaluation and close monitoring is needed. Management should be individually tailored based on clinical findings only [032].

Endoscopic ultrasonography (EUS)

A prolific trend currently designates endoscopic ultrasonography (EUS) literature. It was aimed to record all EUS-studies published during the past decade and evaluate them in terms of scientific quality, creating a stratification based on levels of evidence (LE). All

articles on EUS published between 2001 and 2010 were retrieved using a Pubmed and Cochrane Library search. Inclusion criteria were: original research papers (randomized controlled trials-RCTs, prospective and retrospective studies), meta-analyses, reviews and surveys pertinent to gastrointestinal EUS. Levels of evidence (LE) were assessed using the North of England evidence-based guidelines. Overall, 1,832 eligible articles were reviewed. The majority (46 %) of reports comprised retrospective descriptive studies (LE III). Expert reviews and committee reports (LE IV) accounted for 29 percent, well-designed quasiexperimental studies (LE IIb) for 20 percent, RCTs (LE Ib) for 2.4 percent, prospective controlled trials (LE IIa) for 1.4 percent, and meta-analyses (LE Ia) for 1.1 percent of the total. High LE (Ia-Ib) were assigned to loco-regional staging of luminal gastrointestinal cancers; mediastinal staging of lung cancer; diagnostic work-up of solid pancreatic tumors, suspected biliary obstruction and choledocholithiasis; celiac plexus neurolysis; and pancreatic pseudocysts drainage. Intermediate to low LE (IIa-IV) were assigned to submucosal tumors, pancreatic cysts, chronic pancreatitis and novel therapeutic applications (pancreato-biliary drainage, tumor ablation). It was concluded that diagnostic and staging EUS has matured and has proven its clinical impact on patient management. Therapeutic or interventional EUS is still evolving and more quality research and data are needed to establish EUS as the best next intervention to perform once firm evidence is available [033]

Secretin stimulation at endoscopic ultrasound

Endoscopic ultrasound (EUS) evaluation of pancreatic duct compliance after secretin stimulation (sEUS) along with EUS morphologic examination (EUS) and duodenal fluid bicarbonate measurement (endoscopic pancreatic function test, ePFT) in 1 endoscopic session has not been reported as a means of evaluating for chronic pancreatitis (CP). It was evaluated the feasibility of the combined examination and compared EUS measurements of pancreatic ductal compliance with duodenal fluid bicarbonate for diagnosing CP. The study is a prospective case series of patients with suspected CP who underwent a combined EUS. sEUS, and ePFT examination in 1 endoscopic session. The main outcome measures were the feasibility of performing the combination examination and the correlation between ductal compliance and ePFT. All examinations were completed in 1 endoscopic session, and there were no complications in 35 patients. Although there was a trend toward less change from baseline head and body ductal diameter in patients with CP, only the percent change from baseline in the tail was significant (CP 144 % vs healthy patients 241 %). Regression analysis demonstrated fair correlation between maximum change in ductal diameter and duodenal fluid bicarbonate. It was concluded that combined EUS, sEUS, and ePFTs are feasible and safe, with preliminary results demonstrating a positive correlation between pancreatic ductal compliance and duodenal fluid bicarbonate [034].

EUS-FNA

Digital image analysis (DIA) and fluorescence in situ hybridization (FISH) can be used to evaluate biliary strictures with greater accuracy than conventional cytology (CC). We performed a prospective evaluation of the accuracy of CC, compared with that of DIA and FISH, in detection of malignancy in patients undergoing endoscopic ultrasonography (EUS) fine-needle aspiration (FNA). It was collected a minimum of 6 FNA samples from each of 250 patients during EUS. CC or DIA and FISH analyses were performed on every other specimen (from every other FNA pass); patients were randomly assigned to the first test performed. CC slides were reviewed by gastrointestinal cytopathologists who were blinded to all data. Findings from cytohistologic analysis, after a minimum 24-month follow-up period, were used as the standard (n=202; median age, 65 years). Aspirates were collected from lymph nodes (n=111), pancreas (n=61), gastrointestinal lumen wall (n=9), periluminal mass

(n=4), liver (n=8), and miscellaneous sites (n=9). Matched samples provided a mean of 3.2 passes for CC and 1.6 passes for DIA and FISH. The data indicate a potential lack of utility for DIA. The combination of CC and FISH detected malignancy with 11 percent greater sensitivity than CC alone but specificity was reduced from 100 to 96 percent. It was concluded that FISH analysis identifies neoplastic lesions with significantly greater sensitivity than CC in patients with diverse pathologies who underwent EUS with FNA, despite limited tissue sampling for FISH analysis [035].

Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) is a safe and effective method for obtaining samples for cytological diagnosis. Pancreatic cancer is extremely serious and often extremely aggressive, so early detection and diagnosis is important. Therefore, it was actively perform EUS FNA for pathological diagnosis of cancer of digestive organs, especially the pancreas. EUS-FNA was performed in 67 patients (39 male, 28 female, median age 63 years) from 2007 to 2010 in Kyoto University Hospital. To eliminate both quantitatively and qualitatively inadequate samples, it was performed EUS-FNA with rapid on-site cytology. Two squash preparations of the collected cells from biopsy were retrieved. One was stained on-site with Giemsa for rapid cytology to evaluate the quantity and quality of the cell collection. If necessary, second or third trials were carried out to obtain appropriate samples for final cytology diagnosis. The other was wet-fixed and used for Papanicolaou staining. All 11 cases of inflammatory disease were diagnosed as negative on cytology. Solid-pseudopapillary neoplasm (1 case) and endocrine neoplasms (3 cases) were correctly diagnosed on cytology. In pancreatic cancer, 49 of 52 cases (94 %) were diagnosed as positive, but 3 cases (6 %) were false-negative on cytology. The number of centesis for sampling was once in 21 cases, twice in 26 cases and more than twice in 20 cases. In this study of EUS-FNA, sensitivity was 94 percent and specificity was 100 percent. Results of the examination suggest that the combination of EUS-FNA and rapid on-site cytology is a highly specific and sensitive test for detection of pancreatic cancer, and may contribute to reduce excessive centesis [036].

EUS-guided transluminal cholangiodrainage (EUCD)

ERCP and PTCD are considered the gold standard in the interventional treatment of biliary obstruction, in particular, with palliative intention. If ERCP and PTCD are not possible, an alternative drainage procedure such as the EUS-guided cholangiodrainage (EUCD) can be used. By the mean of a compact review, indication, technique, variants of approach, number of treated patients and therapeutic procedures reported by various authors, success rate, spectrum and management of complications as well as recommendations for an appropriate follow-up-investigation protocol for EUCD is described. EUCD is an interventionally endoscopic/-sonografic procedure, which is used in case of postoperatively changed anatomy of the upper GI tract (BII gastric resection, PPPHR, Whipple procedure, [sub-]total gastrectomy, Roux-en-Y reconstruction) and, thus, if papilla of Vater (papilla) can not be reached or catheterized or if the patient denies PTCD in subjects with recurrent, advanced or metastasized tumor lesion(s) of the upper abdomen, hepatobiliary system as well as pancreas and associated obstruction of the biliary tree <u>+</u> jaundice. EUS-guided transluminal puncture from the upper GI tract into various extra- / intrahepatic segments of the biliary system, recanalization of the tumor stenosis with stent insertion through the access site or bypassing the tumor (stent-based retro- or antegrade drainage of the biliary tree). Derived from this, there are various approaches and procedures – EUCD combined with rendesvouz technique, transhepatically with retro- (permanent hepaticoenterostomy) / antegrade internal drainage, and extrahepatically with antegrade drainage (permanent choledochoenterostomy), which are distinguished according to tumor site, possible direction of translumenal puncture, insertion of a guide wire and final stent placement. Within the spectrum of complications bleeding, perforation, stent dislocation / -migration/-occlusion and slight postinterventional pain are relevant. Currently, approximately 200 cases have

been published worldwide; the clinical experience of the reporting institution is based on more than > 70 interventions. With regard to the limited diffusion process, EUCD cannot be considered a standard procedure yet. The advantages comprise low tissue trauma, primary internal drainage and the possible endoscopic re-intervention in case of complications. The high technical challenge in performing EUCD is a disfavourable aspect for broader use in clinical practice. However, the disclosed treatment results demonstrating an acceptable complication rate show that EUCD can be competitively considered to ERCP und PTCD with a great chance for primary success. Thus, EUCD is an elegant, not yet fully established, but rather still experimental procedure of interventional endoscopy/EUS, which needs great expertise of the endoscopist in an interdisciplinary centre of visceral medicine as one of the main predictions. In experienced hands, a safe procedure can be provided, for which a systematic follow-up and a multicentre evaluation of periinterventional management are still needed in order to achieve a final assessment of EUCD for guideline approval [037].

EUS-guided anterograde cholangiopancreatography in failed ERCP

ERCP may be challenging or may fail in certain situations, including postsurgical anatomy, periampullary diverticula, ampullary tumor invasion, and high-grade strictures. To report a large experience with EUS-guided anterograde cholangiopancreatography (EACP) to facilitate ductal access or perform direct EUS-guided therapy in patients with postsurgical anatomy or failed ERCP a retrospective cohort study of 95 consecutive patients with failed ERCP or inaccessible papilla over a 4-year period was presented. EACP techniques involved ductal puncture and ductography, followed by either guidewire advancement for rendezvous ERCP in patients with duodenoscope accessible papilla or direct drainage in altered anatomy. For failures, crossover to the alternate EACP technique was performed when appropriate. EACP procedures were attempted in 95 of 2566 ERCP procedures (4 %). EUSguided cholangiography (n=70) and pancreatography (n=25) were successful in 97 percent and 100 percent, respectively. EUS-guided rendezvous ERCP was successful in 75 percent of biliary procedures and in 56 percent of pancreatic procedures. Direct EUS-guided therapy was successful in 86 percent and 75 percent of biliary and pancreatic procedures, respectively. Direct interventions included pancreaticogastrostomy (n=10), anterograde stent across stricture (n=10), hepaticogastrostomy (n=8), and choledochoduodenostomy (n=1). Ten complications (11 %) related to EACP or subsequent rendezvous ERCP included pancreatitis (n=5), hematoma (n=1), bile leak (n=1), bacteremia (n=1), pneumoperitoneum (n=1), and perforation (n=1). It was concluded that EACP complements ERCP and allows successful pancreaticobiliary therapy in a large proportion of patients with failed ERCP or difficult-to-access papilla [038].

EUS-guided elastography

By using strain assessment, real-time endoscopic ultrasound (EUS) elastography provides additional information about a lesion's characteristics in the pancreas. It was assessed the accuracy of real-time EUS elastography in focal pancreatic lesions using computer-aided diagnosis by artificial neural network analysis. It was performed a prospective, blinded, multicentric study at of 258 patients (774 recordings from EUS elastography) who were diagnosed with chronic pancreatitis (n=47) or pancreatic adenocarcinoma (n=211) from 13 tertiary academic medical centers in Europe (the European EUS Elastography Multicentric Study Group). It was used postprocessing software analysis to compute individual frames of elastography movies recorded by retrieving hue histogram data from a dynamic sequence of EUS elastography into a numeric matrix. The data then were analyzed in an extended neural network analysis, to automatically differentiate benign from malignant patterns. The neural computing approach had 91 percent training accuracy (95 % confidence interval 89 to 92 %) and 84 percent testing accuracy. These results were obtained using the 10-fold cross-validation technique. The statistical analysis of the classification process showed a sensitivity

of 88 percent, a specificity of 83 percent, a positive predictive value of 96 percent, and a negative predictive value of 57 percent. Moreover, the corresponding area under the receiver operating characteristic curve was 0.94 which was significantly higher than the values obtained by simple mean hue histogram analysis, for which the area under the receiver operating characteristic was 0.85. It was concluded that the use of the artificial intelligence methodology via artificial neural networks supports the medical decision process, providing fast and accurate diagnoses [039].

Self-expandable metal stent placement

Pancreatitis is one of complications after self-expandable metal stent (SEMS) placement. The purpose of this study was to evaluate risk factors for pancreatitis after endoscopic SEMS placement for malignant biliary obstruction (MBO). It was retrospectively reviewed 370 consecutive patients who underwent initial transpapillary SEMS placement for biliary decompression. The characteristics of inserted SEMSs were classified according to axial and radial force. Pancreatitis following SEMS insertion was observed in 22 patients (6 %). All of them were mild according to consensus criteria. Univariate analysis indicated that injections of contrast into the pancreatic duct (frequency of pancreatitis, 10%), the placement of an SEMS with high axial force (8 %), and nonpancreatic cancer (16 %) significantly contributed to the development of pancreatitis, whereas female gender, a younger age, a covered SEMS, and a SEMS with high radial force or without a biliary sphincterotomy did not. In a multivariate risk model, SEMSs with high axial force (odds ratio 3.69) and nonpancreatic cancer (OR, 5.52) were significant risk factors for pancreatitis. It was concluded that SEMSs with high axial force and an etiology of MBO other than pancreatic cancer were strongly associated with a high incidence of pancreatitis following transpapillary SEMS placement in patients with distal malignant biliary obstruction [040].

Endoscopic biliary stenting is a well-established palliative treatment in patients with unresectable malignant biliary strictures. Obstruction of uncovered self-expanding metal stent (SEMS) due to tumor ingrowth is the most frequent complication. Partially covered SEMS might increase stent patency but could favor complications related to stent covering, such as pancreatitis, cholecystitis, and migration. The aim of one study was to evaluate the efficacy and safety of partially covered SEMS in patients with an unresectable malignant stricture. Patients with malignant extrahepatic biliary obstruction treated biliarv endoscopically with partially covered SEMS were included in this multicenter, prospective, nonrandomized study. One hundred ninety-nine patients were endoscopically treated with partially covered SEMS in 32 Spanish hospitals. Clinical success after deep cannulation was 96 percent. Early complications occurred in 4 percent (3 pancreatitis, 2 cholangitis, 1 hemorrhage, 1 perforation, and 1 cholecystitis). Late complications occurred in 20 percent (18 obstructions, 10 migrations, 6 cholangitis without obstruction, 3 acute cholecystitis, and 2 pancreatitis), with no tumor ingrowth in any case. Median stent patency was 139 ± 113 days. One-year actuarial probability of stent patency was 70 percent and that of nonmigration was 86 percent. Multivariate analysis showed adjuvant radio- or chemotherapy as the only independent predictive factor of stent patency and previous insertion of a biliary stent was the only predictive factor of migration. It was concluded that the partially covered SEMS was easily inserted, had a high clinical success rate, and prevented tumor ingrowth. The incidence of possible complications related to stent coverage, namely, migration, pancreatitis, and cholecystitis, was lower than in previously published series [041].

Colonization of pancreatic stents

Pancreatic stents (PSs) are commonly inserted at the time of endoscopic retrograde cholangiopancreatography to reduce the risk of pancreatitis. If left in situ for more than two

weeks, they have been associated with pancreatic duct injury. The mechanism of this injury is not clear, but it may be related to bacterial colonization. To determine the incidence of PS colonization by microorganisms and the relationship between such colonization and the type, length, diameter, and duration of PSs in situ series of endoscopic retrograde cholangiopancreatographies performed by a single operator in a tertiary referral centre during which a PS was placed was analysed. In each case, after removing the PS, the segment of the PS, which had been intraluminal, was sent for microbiological analysis. Microscopy and culture results were compared with stent length (cm), time in situ (d), demographic information, and clinical course. Of the 47 PSs sent for culture, 28 grew clinically significant bacteria. The majority of organisms cultured were of the Klebsiella, Escherichia, Enterobacter, and Enterococcus genera. Time in situ was found to correlate strongly with the growth of clinically significant organisms using a logarithmic regression analysis tool. In addition, 1 patient developed Enterobacter septicaemia almost certainly related to stent colonization, which necessitated urgent removal of the stent 10 days after insertion. It was concluded that colonization of PSs by pathogenic organisms is common and related to duration in situ of the PS. Enteric organisms are frequently implicated. Although significant clinical sequelae are infrequent, we suggest that PSs should not be left in situ for >7 to 10 days due to the significant risk of bacterial colonization [042].

OTHER DIAGNOSTICS

СТ

Multidetector CT is a valuable technique for diagnosis/staging in several pancreatic pathologies. Diagnosis is usually based on tissue density measurements. Recently, newer functional CT techniques have been introduced. The aim of one study was to assess variability in perfusion and dual-energy CT data, and to compare these data with density measurements in the pancreas of a healthy population. Two groups were included: 20 patients underwent perfusion CT imaging, and 10 patients were scanned using a dual-energy protocol. In both groups, tissue density (Hounsfield units, HU) was measured in the pancreatic head, body and tail. Functional data were calculated (blood flow/blood volume in the perfusion CT group, iodine concentration in the dual-energy group), and variability was assessed. Density measurements were comparable for the perfusion and dual-energy CT groups, and ranged from 14 to 60 HU. Maximal enhancement differences between the head/body/tail of the pancreas ranged between 2 and 21 HU. Considerable variability was observed, both in density measurements (ranging from 3 to 34 %) and in functional parameters (mean variability in perfusion CT parameters blood flow and blood volume was 21 and 10 % respectively; mean variability in dual-energy iodine-mapping results was 24 %). The study demonstrated the presence of important intraindividual variability in pancreatic tissue contrast enhancement, regardless of the CT technique used. Considering the variability observed in this study, the use of cut-off values to characterize pancreatic pathologies seems troublesome, and morphologic primary and secondary changes will remain important, even when using novel functional imaging techniques. and IAP [043].

Diffusion-weighted imaging (DWI)

It was aimed to explore the role of diffusion-weighted imaging (DWI) in the discrimination of pancreatic lesions through meta-analysis. The MEDLINE, EMBASE, Cancerlit, and Cochrane Library databases, from 2001 to August 2011, were searched for studies evaluating the diagnostic performance of DWI in the discrimination of pancreatic lesions. It was determined sensitivities and specificities across studies, calculated positive and negative likelihood ratios (LR+ and LR-), and constructed summary receiver operating characteristic curves. A total of 11 studies with 586 patients, who fulfilled all of the inclusion criteria, were considered for the analysis. No publication bias was found. The pooled sensitivity of DWI was 0.86 (95 % confidence interval 0.78 to 0.91) and the pooled specificity was 0.91. Overall, LR+ was 9.8 and LR- was 0.15. The area under the curve of the summary receiver operating characteristic was 0.94. In subgroup analysis, prospectively designed studies had the highest pooled sensitivity (0.87) and specificity (0.96). Study sensitivity was not correlated with the prevalence of pancreatic lesions. It was concluded that a limited number of small studies suggest that DWI is a potentially technically feasible measure to differentiate malignant from benign pancreatic lesions. However, it is still controversial and is limited in that it can only distinguish certain lesions. High-quality prospective studies on DWI for the discrimination of pancreatic lesions still need to be conducted [044].

Secretin-enhanced MRCP

The purpose of one article was to present a proposal for quantification of exocrine function using secretin-enhanced MRCP for the diagnosis of chronic pancreatitis. The article also reviewed the technique and application of secretin-enhanced MRCP in evaluating various pancreatic abnormalities. One hundred thirty-four consecutive patients with chronic abdominal pain undergoing secretin-enhanced MRCP for suspected chronic pancreatitis

were included. Patients were divided into four clinical groups (normal, equivocal, early chronic pancreatitis, established pancreatitis) on the basis of clinical symptoms and additional investigations, including CT (n=98), endoscopic pancreatic function test (n=65), endoscopic ultrasound (n=84), and ERCP (n=36). The volume of secretion was obtained by drawing a region of interest around T2 bright fluid secreted on postsecretin HASTE images. The maximal rate of secretion in response to secretin was obtained by plotting change in signal intensity on sequential postsecretin images. The analysis of variance test was used to compare the clinical groups with the volume and rate of secretion. Significant volume differences were found between the normal and established pancreatitis groups as well as the equivocal and established pancreatitis groups. Marginally significant differences were found between the normal and early pancreatitis groups as well as early and established pancreatitis groups. Differences in the maximal rate of secretion were not statistically significant. Secretory volume measurement of secretin-enhanced MRCP data is a simple method that brings out significant differences between normal, early, and established pancreatitis patients [045].

Proton magnetic resonance spectroscopy

To characterize normal pancreas metabolites using in vivo proton magnetic resonance spectroscopy (¹H MRS) at 3T under conditions of breath-holding and free-breathing. The pancreases of 32 healthy volunteers were examined using ¹H MRS during breath-holding and free-breathing acquisitions in a single-voxel point-resolved selective spectroscopy sequence (PRESS) technique using a 3T MRI system. Resonances were compared between paired spectra of the two breathing modes. Furthermore, correlations between lipid (Lip) content and age, body-mass index (BMI), as well as choline (Cho) peak visibility of the normal pancreas were analysed during breath-holding. Twenty-nine pairs of spectra were successfully obtained showing three major resonances, Lip, Cho, cholesterol and the unsaturated parts of the olefinic region of fatty acids (Chol+Unsat). Breath-hold spectra were generally better, with higher signal-to-noise ratios and Cho peak visible status. Correlations were significant between spectra acquired by the two breathing modes, especially for Lip height, Lip area, and the area of other peaks at 1.9-4.1 ppm. However, the Lip resonance was significantly different between the spectra of the two breathing modes. In the breathholding spectra, there were significant positive correlations between Lip peak height, area, and age, but not between Lip peak area and BMI. There was no statistical difference in Cho resonances between males and females. The Lip peak height and area were significantly higher in the Cho peak invisible group than in the Cho peak visible group. In vivo ¹H MRS of the normal pancreas at 3T is technically feasible and can characterize several metabolites. ¹H MRS during breath-holding acquisition is superior to that during free-breathing acquisition [046].

Ultrasound based acoustic radiation force impulse (ARFI)

To prospectively assess the accuracy of per-abdominal US elastography in the form of acoustic radiation force impulse – virtual touch tissue quantification (ARFI-VTQ) and eSie touch elasticity imaging in characterizing and differentiating inflammatory pancreatic diseases. One-hundred and sixty-six patients from among the patients during the period April 2009 to December 2010, for master health check-up, blood donation and those with pancreatic pathology. Based on the clinical symptomatic criteria and diagnostic imaging findings, the patients were divided into normal, chronic and acute, or acute resolving, pancreatitis group. The ultrasound based ARFI-VTQ and eSie touch elasticity imaging techniques were applied. The mean ARFI-VTQ values were 1.28 m/s, 1.25 m/s and 3.28 m/s for the normal, chronic and acute pancreas, respectively. The eSie touch gray scale and

color elastograms were light gray and purple-greenish, respectively for both normal and chronic pancreas, while for acute pancreas the elastograms were dark black on the gray scale and orange to red on color scale. Both the ARFI-VTQ and eSie touch elasticity imaging techniques may be successfully adopted in order to diagnose acute pancreatitis, to assess extent of inflammation (whether focal or diffuse), to assess peripancreatic edema, to identify presence of necrotic areas and early pseudocyst formation, to early diagnose acute recurrent attacks and to monitor patient's response to treatment [047].

ACUTE PANCREATITIS

Background to revision of Atlanta classification

The need to accurately classify the severity of patients with acute pancreatitis is widely acknowledged but some questions pertinent to this remain debatable. The aim of this study was to benchmark opinions of pancreatologists worldwide with regard to the issues related to classifying the severity of acute pancreatitis. An online survey was conducted using an independent commercial service. The corresponding authors of all articles pertinent to clinical aspects of acute pancreatitis published over the last 5 years were invited to participate. A total of 528 invitations were sent and 240 (45 %) responses from 49 countries, representing all the inhabited continents, were received. The Atlanta approach to classifying the severity of acute pancreatitis was considered adequate for modern clinical practice and clinical research by 40 (17 %) of the respondents. The determinants-based approach to classifying the severity of acute pancreatitis was considered adequate for modern clinical practice and clinical research by 188 (78 %) and 191 (80 %) of the respondents, respectively. The definitions of local and systemic determinants of severity were also clarified. Classifying the severity of acute pancreatitis on the basis of Atlanta approach was considered inadequate by the overwhelming majority of respondents. An international consensus on the new classification of severity of acute pancreatitis has to take into account the results of this survey [048].

Imaging of acute pancreatitis requires not only an understanding of the disease subtypes and the myriad of associated complications but also familiarity with the appropriate radiologic nomenclature as defined by the Atlanta symposium in 1992 and, more recently, by the Acute Pancreatitis Classification Working Group in 2008. The accurate description of the radiological findings plays a critical role in the evaluation and management of patients with acute pancreatitis, particularly those with severe disease. There have been increasing efforts to develop uniformity in the use of terminology used to define the radiologic findings in acute pancreatitis, in particular, the terminology for fluid collections, a common area of inconsistency and confusion. Terms such as "acute peripancreatic fluid collections," "acute post- necrotic fluid collections," "pseudocyst," and "walled-off pancreatic necrosis" are now recommended as they describe the evolution of fluid collections in patients with both interstitial and necrotizing pancreatitis and nonspecific terms such as "pancreatic abscess" and "phlegmon" are being abandoned. In one review it was illustrated, with case examples, the standardized terminology used in the radiological and clinical description of acute pancreatitis, its severity, and complications with an emphasis on the role of ultrasound, computed tomography and magnetic resonance imaging. Different management options of the associated complications are also discussed. The use of standardized terminology will hopefully improve the communication between radiologists, gastroenterologists, and surgeons to facilitate treatment planning and will lead to enhanced outcomes for patients with acute pancreatitis as well as create uniformity for enrollment into research studies [049].

The revised Atlanta classification of acute pancreatitis

An international working group has modified the Atlanta classification for acute pancreatitis to update the terminology and provide simple functional clinical and morphologic classifications. The modifications

- address the clinical course and severity of disease
- divide acute pancreatitis into interstitial edematous pancreatitis and necrotizing pancreatitis
- distinguish an early phase (1st week) and a late phase (after the 1st week)

- emphasize systemic inflammatory response syndrome and multisystem organ failure.

In the 1st week, only clinical parameters are important for treatment planning. After the 1st week, morphologic criteria defined on the basis of computed tomographic findings are combined with clinical parameters to help determine care. This revised classification introduces new terminology for pancreatic fluid collections. Depending on presence or absence of necrosis, acute collections in the first 4 weeks are called acute necrotic collections or acute peripancreatic fluid collections. Once an enhancing capsule develops, persistent acute peripancreatic fluid collections are referred to as pseudocysts; and acute necrotic collections, as walled-off necroses. All can be sterile or infected. Terms such as pancreatic abscess and intrapancreatic pseudocyst have been abandoned. The goal is for radiologists, gastroenterologists, surgeons, and pathologists to use the revised classifications to standardize imaging terminology to facilitate treatment planning and enable precise comparison of results among different departments and institutions [050].

Scoring system

The early identification of clinically severe acute pancreatitis (AP) is critical for the triage and treatment of patients. The aim of one study was to compare the accuracy of computed tomography (CT) and clinical scoring systems for predicting the severity of AP on admission. Demographic, clinical, and laboratory data of all consecutive patients with a primary diagnosis of AP during a two-and-half-year period was prospectively collected for this study. A retrospective analysis of the abdominal CT data was performed. Seven CT scoring systems (CT severity index (CTSI), modified CT severity index (MCTSI), pancreatic size index (PSI), extrapancreatic score (EP), "extrapancreatic inflammation on CT" score (EPIC), "mesenteric oedema and peritoneal fluid" score (MOP), and Balthazar grade) as well as two clinical scoring systems; Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II and Bedside Index for Severity in AP (BISAP) were comparatively evaluated with regard to their ability to predict the severity of AP on admission (first 24 h of hospitalization). Clinically severe AP was defined as one or more of the following: mortality, persistent organ failure and/or the presence of local pancreatic complications that require intervention. All CT scans were reviewed in consensus by two radiologists, each blinded to patient outcome. The accuracy of each imaging and clinical scoring system for predicting the severity of AP was assessed using receiver operating curve analysis. Of 346 consecutive episodes of AP, there were 159 (46 %) episodes in 150 patients (84 men, 66 women; mean age, 54 years; age range, 21-91 years) who were evaluated with a contrast-enhanced CT scan (n=131 episodes) or an unenhanced CT scan (n=28 episodes) on the first day of admission. Clinically severe AP was diagnosed in 29/159 (18 %) episodes; 9 (6 %) patients died. Overall, the Balthazar grading system (any CT technique) and CTSI (contrast-enhanced CT only) demonstrated the highest accuracy among the CT scoring systems for predicting severity, but this was not statistically significant. There were no statistically significant differences between the predictive accuracies of CT and clinical scoring systems. It was concluded that the predictive accuracy of CT scoring systems for severity of AP is similar to clinical scoring systems. Hence, a CT on admission solely for severity assessment in AP is not recommended [051].

Blood glucose as predictor of severity

The objective of one study was to retrospectively analyze the association of mean glucose level (MGL) and glycemic lability index (GLI; as a measure of glucose variability) with intensive care unit (ICU) mortality in patients with severe acute pancreatitis (SAP). Paperbased medical records of patients with SAP who were admitted to an ICU 2005 to 2010 were analyzed. Glucose measurements, demographic characteristics, clinical features, data on the first and second 24-hour Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and outcomes were obtained. Time-weighted glucose parameters were used. A total of 294 patients with 34,796 glucose measurements were included in the final analysis. The time-weighted MGL was 9.31 ± 1.91 mmol/L, and the median of GLI was 55.27 (mmol/L per h and week. Intensive care unit mortality was 44 percent and increased progressively as GL increased, reaching 63 percent of patients with GLI above 115.89 (mmol/L per h and wwek. The highest odds ratio for ICU death was found in patients with the highest quartile of GLI: odds ratio, 3.47 (95 % confidence interval, 1.76 to 6.86). No such relationship could be found with MGL. Glycemic lability index was better able to predict ICU death than was MGL (the area under the curves were 0.642 vs 0.561, respectively). The logistic regression analysis showed that GLI, the second 24-hour APACHE II score, and the number of organ failures upon ICU admission contributed independently to the risk of mortality. It was observed that GLI was a better predictor of ICU and hospital mortality than was MGL. Together with the second 24-hour APACHE II score and the number of organ failures upon ICU admission, GLI is an independent predictor of mortality in patients with SAP [052].

Guidelines

The elaboration and publication of guidelines should help homogenizing the management of frequent diseases with high mortality and morbidity rates, such as acute pancreatitis. In 2001 (before the Consensus Conference) and 2008, the same questionnaire dealing with recommendations for AP management was sent to the French gastroenterology Units. To evaluate the implementation of French guidelines on the management of acute pancreatitis (AP), and to correlate changes with a received medical training course responses in 2001 and 2008 were compared. One hundred and seventy-six questionnaires were analyzed (public hospitals: 62 %, academic hospitals: 20 %, private institutions: 18 %). In 2008 (vs 2001). lipase levels were measured for establishing AP diagnosis by 99 percent (vs 83 %). To evaluate AP severity, a computed tomography (CT) scan was performed at 48 h by 69 percent (vs 29 %). The most used severity index was the CT Balthazar score 76 percent (vs 55 %). Antibiotic prophylaxis and artificial nutrition by enteral route were proposed by 20 percent (vs 57 %) and 58 percent (vs 25 %) for necrotizing pancreatitis. Practices were more frequently in agreement with the guidelines in public nonacademic and academic hospitals. Training course on AP management was associated with a more appropriate use of CT scan for the evaluation of AP severity and of antibiotics. Thus, major changes were noticed since the publication of the French guidelines. Although establishing guidelines is an expensive process, it does increase compliance with best evidence-based practice [053].

Epidemiology

It was identified admissions with primary diagnosis of acute pancreatitis (AP) in Nationwide Inpatient Sample between 1998 and 2007. Idiopathic AP was defined as all cases after excluding International Classification of Diseases, Ninth Revision, codes for other causes of AP (including biliary, alcoholic, trauma, iatrogenic, hyperparathyroidism, hyperlipidemia, etc). Among the primary admissions for AP, 27 percent had biliary pancreatitis, 25 percent alcoholic, and 37 percent idiopathic. Idiopathic AP had estimated 81,8025 admissions with a mean hospitalization of 6 days. Patients with IAP accounted for almost half of the fatalities among the cases of AP (48 %) and had a higher mortality rate than both patients with biliary pancreatitis and patients with alcoholic pancreatitis (1.9 %, 1.5 %, and 1.0 %, respectively). Forty-six percent of patients with biliary pancreatitis underwent cholecystectomy during the index hospitalization, compared with 0.42 percent of patients with IAP. Patients with IAP had a demographic distribution similar to that of patients with biliary AP (female predominant and older), which was distinct from patients with alcoholic pancreatitis (male predominant and younger). There was a gradual but steady decrease in the incidence of IAP, from 41 percent in 1998 to 30 percent in 2007. Thus, despite improving diagnostics, IAP remains a common clinical problem with a significant mortality. Standardization of the clinical management of these patients warrants further investigation [054].

Importance of age

The aim of one study was to investigate the overall clinical characteristics of elderly patients with acute pancreatitis. It was retrospectively evaluated 227 consecutively enrolled patients who were admitted with acute pancreatitis. The clinical features, the radiological and laboratory data and the clinical outcome were analyzed according to the age groups (\geq 65 years vs <65 years). Among the 227 enrolled patients with acute pancreatitis, there were 85 elderly patients and 142 non-elderly. The mean age of the elderly patients was 72 ± 6 years and that of the non-elderly was 45 ± 12. For the elderly patients, biliary pancreatitis was the most common cause (57 %), but alcoholic pancreatitis was most common in the non-elderly patients (46 %). Although the computed tomography (CT) severity index was significantly higher for the non-elderly patients, the acute physiology and chronic health evaluation (APACHE II) score was significantly higher for the elderly than that for the non-elderly. However, the duration of the hospital stay (10 ± 10 days vs 12 ± 10 days) and mortality (3.5 % vs 0.7 %) were not different between the age-groups. In the study, chronological age had no significant influence on the clinical outcome in spite of the different etiologies and severity of acute pancreatitis [055].

Diagnostics

Acute pancreatitis is an acute inflammatory condition of the pancreas, which might extend to local and distant extrapancreatic tissues. The global incidence varies between 18 and 73 cases per 100,000 and the pathogenesis recognizes alcohol exposure and biliary tract disease as the leading causes, ahead of post-endoscopic retrograde cholangiopancreatography, drugs and abdominal trauma. The diagnosis of acute pancreatitis is substantially based on a combination of clinical signs and symptoms, imaging techniques and laboratory investigations. Contrast-enhanced computed tomography is the reference standard for the diagnosis, as well as for establishing disease severity. The assessment of pancreatic enzymes, early released from necrotic tissue, is the cornerstone of laboratory diagnosis in this clinical setting. Although there is no single test that shows optimal diagnostic accuracy, most current guidelines and recommendations indicate that lipase should be preferred over total and pancreatic amylase. Although a definitive diagnostic threshold cannot be identified, cut-offs comprised between ≥ 2 and ≥ 4 times the upper limit of the reference interval are preferable. The combination of amylase and lipase has been discouraged as although it marginally improves the diagnostic efficiency of either marker alone, it increases the cost of investigation. Some interesting biomarkers have been also suggested (e.g., serum and urinary trypsinogen-1, -2 and -3, phospholipase A2, pancreatic elastase, procalcitonin, trypsinogen activated protein, activation peptide of carboxypeptidase B, trypsin-2-alpha1 antitrypsin complex and circulating DNA), but none of them has found widespread application for a variety of reasons, including the inferior diagnostic accuracy when compared with the traditional enzymes, the use of cumbersome techniques, or their recent discovery. The promising results of recent proteomics studies showed that this innovative technique might allow the identification of changes characterizing pancreatic tissue injury, thus highlighting new potential biomarkers of acute pancreatitis [056].

MRI

The aim of one study was to retrospectively measure and compare pancreatic apparent diffusion coefficient (ADC) in patients with acute pancreatitis (AP) with aged matched controls who underwent diffusion weighted imaging (DWI). Pancreatic ADC values from 27 patients with a clinical diagnosis of AP and 38 normal age-matched controls evaluated with DWI (b = 0 and 800 mm²/s) were retrospectively and independently measured by two radiologists. The ADCs were compared between the groups and between each of the pancreatic segments in the normal group. Inter-observer reliability was calculated and receiver operating characteristic analysis was used to determine the sensitivity and specificity of DW imaging in the diagnosis of acute pancreatitis. The ICC for inter-observer reliability was 0.98 in the control and 0.97 in the AP group. The mean pancreatic ADC in the AP group was significantly lower than in the normal group. There was no significant difference in mean ADCs between each of the pancreatic segments in the controls. A threshold ADC value yielded a sensitivity of 93 percent and specificity of 87 percent for detecting acute pancreatitis for b values of 0 and 800 s/mm². Pancreatic apparent diffusion coefficients are significantly lower in patients with acute pancreatitis than normal controls [057].

Smoking

Several studies have shown that smoking increases the risk of chronic pancreatitis. However, the impact of smoking on the development of acute pancreatitis has not been fully studied. To clarify the association between cigarette smoking, smoking cessation and the risk of acute pancreatitis a follow-up study was conducted of 84,667 Swedish women and men, aged 46-84, during 12 years to study the association between smoking status, smoking intensity and duration, duration of smoking cessation and the risk of acute pancreatitis. Only those with the first event of the disease and no previous history of acute pancreatitis were included. Cox proportional hazards models were used to estimate rate ratios (RRs) with 95 percent confidence intervals for different smoking-related variables, adjusted for age, gender, body mass index, diabetes, educational level and alcohol consumption. In total, 307 cases with non-gallstone-related and 234 cases with gallstone-related acute pancreatitis were identified. The risk of non-gallstone-related acute pancreatitis was more than double (RR=2.29; 95 % confidence interval 1.63 to 3.22) among current smokers with ≥20 packyears of smoking as compared with never-smokers. The corresponding risk among individuals with ≥400 g monthly consumption of alcohol was increased more than fourfold (RR=4.12; 95 % confidence interval 1.98 to 8.60). The duration of smoking rather than smoking intensity increased the risk of non-gallstone-related acute pancreatitis. After two decades of smoking cessation the risk of non-gallstone-related acute pancreatitis was reduced to a level comparable to that of non-smokers. There was no association between smoking and gallstone-related acute pancreatitis. Smoking is an important risk factor for nongallstone-related acute pancreatitis. Early smoking cessation should be recommended as a part of the clinical management of patients with acute pancreatitis [058].

SPINK-1

Serine protease inhibitor Kazal type 1 (SPINK1) protects against premature intracellular activation of trypsinogen and development of acute pancreatitis. Our aim was to determine the prevalence of SPINK1 mutations in unselected patients with first-time acute pancreatitis and in the Danish background population in a meta-analysis to combine the results with findings in similar investigations worldwide and to evaluate whether patients with SPINK1 mutations had a more severe clinical course. A total of 75 consecutive patients admitted to a

surgical department with first-time acute pancreatitis were prospectively included. In addition, 188 healthy controls were tested for the SPINK1 variants: p.N34S, p.P55S, p.R65Q, p.R67C, and IVS3+2 T>C, in order to calculate the prevalence of SPINK1 mutations in the Danish background population. A meta-analysis was conducted on previous studies on acute pancreatitis and SPINK1 mutations. Two patients (3 %) and two controls (1 %) were heterozygous for the p.N34S variant. The meta-analysis confirmed that the p.N34S variant is overrepresented in patients with acute pancreatitis compared with the background population (OR=3.16). But this analysis did not clarify whether this was only true for patients with first-time acute pancreatitis or recurrent pancreatitis as the present studies do not provide this information, and those who do not have enough patients to reach levels of statistic significance, even if data are pooled. It was concluded that the SPINK1 variant p.N34S is overrepresented in patients with acute pancreatitis, but more studies distinguishing between first-time and recurrent acute pancreatitis have to be done to determine whether this is only true for patients with recurrent acute pancreatitis [059].

Cytokines

It was aimed at synchronously examining the early time course of 4 proinflammatory cytokines as predictive factors for development of organ failure in patients with acute pancreatitis (AP). Interleukin (IL) 6, IL-8, IL-18, and tumor necrosis factor α were measured on admission and at days 1, 2, and 14 in 60 patients admitted with first attack of AP. The prediction of single-organ and multiorgan failure from the cytokine profiles was evaluated by receiver operating characteristic analyses. Interleukin 6 and IL-8 levels were significantly higher in patients who developed renal, respiratory, and circulatory failure, as was the case for patients with multiorgan failure. Interleukin 18 levels were significantly elevated in renal and respiratory failure only. Tumor necrosis factor α was significantly elevated in all types of organ failures, except for intestinal failure. It was concluded that synchronous measurements of 4 cytokines demonstrated IL-6 and IL-8 to be predictive as early surrogate markers with regard to organ failures in AP. The fact that all of the cytokines were particularly elevated in patients with organ failures calls for evaluation of agents modifying the severe inflammatory response in patients with AP [060].

Moderately severe acute pancreatitis

It was described the entity moderately severe acute pancreatitis (MSAP), characterized by local complications (LCs) without organ failure (OF). The aim of one study was to validate MSAP. It was classified a prospectively collected cohort of 137 acute pancreatitis patients admitted to Mayo Clinic Hospitals into severe acute pancreatitis (SAP; n=15), presence of OF with/without LCs; MSAP (n=27), presence of LCs without OF; and mild acute pancreatitis (MAP; n=95), no OF and LCs. Primary outcomes were need for intensive care unit (ICU) care, total ICU days, total hospital stay, need for interventions, and death. Scores in the Acute Physiology and Chronic Health Evaluation II during admission were significantly different among the 3 groups; scores in the systemic inflammatory response syndrome during admission were similar between MAP and MSAP. Compared with patients with MAP, patients with MSAP had a significantly longer hospital stay (4 vs 6 days). Compared with those with SAP, a significantly smaller proportion of patients with MSAP required ICU care (12 % vs 80 %); total hospital stay and need for interventions were similar (6 vs 21 days and 44 % vs 33 %, respectively). None of the MSAP patients died compared with 40 percent from the SAP group. It was concluded that MSAPcan be validated as an exclusive entity [061].

Acute biliary pancreatitis

To establish a practical and effective clinical pathway (CP) for the etiological diagnosis of acute biliary pancreatitis a total of 2216 patients enrolled were randomly divided into control group (n=1120) and CP group (n=1096) according to different etiological diagnosis methods including following doctor's established experiences and habits and the designed CP in the study. There was no significant difference in baseline data between the two groups. The etiology of acute pancreatitis was determined in 91 percent (999/1096) of cases in the CP group which was significantly higher than the control group (66 %, 734/1120). The enhanced etiological determination of CP group was mainly consisted of the increased detection of biliary stones, duodenal diseases as well as pancreas divisum. The positive etiological determination of magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography in the CP group were 59 percent (273/462) and 86 percent (98/114), respectively. It was concluded that CP established in this study significantly enhances the biliary etiological determination of acute pancreatitis. It is easy to be conducted and may be of importance to improve the quality of etiological diagnosis of acute pancreatitis [062].

To analyze the efficacy of pancreatic duct (PD) stenting following endoscopic sphincterotomy (EST) compared with EST alone in reducing complication rate and improving overall outcome in acute biliary pancreatitis (ABP). Between 2009 and 2010, 141 nonalcoholic patients with clinical, laboratory and imaging evidence of ABP were enrolled. Emergency endoscopic retrograde cholangiopancreatography (ERCP) was performed within 72 h from the onset of pain. Seventy patients underwent successful ERCP, EST, and stone extraction (control group); 71 patients (PD stent group) had EST, stone extraction and small-caliber (5 Fr, 3-5 cm) pancreatic stent insertion. All patients were hospitalized for medical therapy and jejunal feeding and were followed up. The mean age, Glasgow score, symptom to ERCP time, mean amylase and CRP levels at initial presentation were not significantly different in the PD stent group compared to the control group. Complications (admission to intensive care unit, pancreatic necrosis with septicemia, large (>6 cm) pseudocyst formation, need for surgical necrosectomy) were less frequent in the PD stent group resulting in a significantly lower overall complication rate (10 % vs 31 %). Mortality rates (0 % vs 4 %) were comparable, reasonably low and without any significant differences. It was concluded that temporary small-caliber PD stent placement may offer sufficient drainage to reverse the process of ABP. Combined with EST the process results in a significantly less complication rate and better clinical outcome compared with EST alone during the early course of ABP [063].

Timing of cholecystectomy after mild biliary pancreatitis

Although current guidelines recommend performing cholecystectomy early after mild biliary pancreatitis, consensus on the definition of early (i.e. during index admission or within the first weeks after hospital discharge) is lacking. To determine the risk of recurrent biliary events in the period after mild biliary pancreatitis but before interval cholecystectomy and to determine the safety of cholecystectomy during the index admission it was performed a systematic search in PubMed, Embase, and Cochrane for studies published from 1992 to July 2010. Included were cohort studies of patients with mild biliary pancreatitis reporting on the timing of cholecystectomy, number of readmissions for recurrent biliary events before cholecystectomy, operative complications (e.g. bile duct injury, bleeding), and mortality. Study quality and risks of bias were assessed. After screening 2413 studies, 8 cohort studies and 1 randomized trial describing 998 patients were included. Cholecystectomy was performed during index admission in 483 patients (48 %) without any reported readmissions. Interval cholecystectomy was performed in 515 patients (52 %) after 40 days (median; interquartile range: 19-58 days). Before interval cholecystectomy, 95 patients (18 %) were

readmitted for recurrent biliary events (0 % vs 18 %). These included recurrent biliary pancreatitis (n=44 %), acute cholecystitis (n=17), and biliary colics (n=35). Patients who had an endoscopic retrograde cholangiopancreatography had fewer recurrent biliary events (10 % vs 24 %), especially less recurrent biliary pancreatitis (1 % vs 9 %). There were no differences in operative complications, conversion rate (7 %), and mortality (0 %) between index and interval cholecystectomy. Because baseline characteristics were only reported in 26 percent of patients, study populations could not be compared. It was concluded that interval cholecystectomy after mild biliary pancreatitis is associated with a high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. Cholecystectomy during index admission for mild biliary pancreatitis appears safe, but selection bias could not be excluded [064].

Prediction for recurrence

In a population-based study, it was examined recurrence rates of acute pancreatitis (AP) after cholecystectomy performed to prevent recurrences of AP. It was abstracted data from medical records of all residents who underwent cholecystectomy for the management of presumed gallstone or idiopathic AP between 1990 and 2005 (n=239). Based on (i) significantly elevated liver enzymes (≥threefold increase of alanine aminotransferase or aspartate aminotransferase) on day 1 and (ii) the presence of gallstones/sludge in the gall bladder, it was categorized patients into 4 groups: A (i + ii), B (i but not ii), C (ii but not i), and D (neither i nor ii). Recurrence rates of AP after cholecystectomy were determined in all groups. The median follow-up after cholecystectomy was 99 months (range, 8-220). AP recurred in 13 of 142 patients (9 %) in group A, 1 of 17 patients (6 %) in group B, 13 of 57 patients (23 %) in group C, and 14 of 23 patients (61 %) in group D. No difference was seen in recurrence rates in groups A vs. B. Recurrences were more frequent in patients with normal liver enzymes and in patients without sonographic evidence of gallstones/sludge. When AP is associated with significantly elevated liver enzymes on day 1, recurrence rates after cholecystectomy are low (9%). However, postcholecystectomy recurrence rates of AP are high in those without such laboratory abnormalities (34%), especially in those without gall bladder stones/sludge (61%) on abdominal ultrasonography. Our results raise doubts about the efficacy of cholecystectomy to prevent recurrent AP in patients with the absence of either a significant elevation of liver tests on day 1 of AP or gallstones and/or sludge in the gall bladder on initial ultrasound examination [065].

Early cholecystectomy and ERCP

Cholecystectomy is recommended during hospitalizations for acute biliary pancreatitis (ABP). It was sought to assess the population-based effectiveness of index cholecystectomy by using nationwide data in a retrospective, cohort study of all acute-care hospitals in Canada from 2007 to 2010. Among 5646 patients with ABP, 32 percent underwent cholecystectomy and 22 percent ERCP during the index admissions. Patients admitted to hospitals in the highest quartile for cholecystectomy volume were more than 10-fold likely to undergo cholecystectomy during the index admission (adjusted odds ratio 11.0; 95 % confidence interval 7.4 to 16.5). The 12-month readmission rate for ABP was lower with cholecystectomy (6 % vs 14 %) and therapeutic ERCP (5 % vs 13 %). After multivariate adjustment, lower readmission rates were independently associated with both cholecystectomy (adjusted hazard ratio 0.39; 95 % confidence interval 0.32 to 0.48) and ERCP (adjusted HR 0.37). After excluding early readmissions (within 28 days of discharge), the adjusted HR for cholecystectomy was 0.43. The admitting hospital's cholecystectomy volume was inversely associated with 12-month readmission rates for ABP. It was concluded that cholecystectomy and ERCP during the index admission were associated with reduced readmission rates for ABP, providing population-based evidence to support consensus guidelines that recommend early biliary intervention [066].

EST and stenting

To analyze the efficacy of pancreatic duct (PD) stenting following endoscopic sphincterotomy (EST) compared with EST alone in reducing complication rate and improving overall outcome in acute biliary pancreatitis (ABP) 141 nonalcoholic patients with clinical, laboratory and imaging evidence of ABP were enrolled between 2009 and 2010,. Emergency endoscopic retrograde cholangiopancreatography (ERCP) was performed within 72 h from the onset of pain. Seventy patients underwent successful ERCP, EST, and stone extraction (control group); 71 patients (PD stent group) had EST, stone extraction and small-caliber (5 Fr. 3-5 cm) pancreatic stent insertion. All patients were hospitalized for medical therapy and jejunal feeding and were followed up. The mean age, Glasgow score, symptom to ERCP time, mean amylase and CRP levels at initial presentation were not significantly different in the PD stent group compared to the control group: 61 versus. 64, 3.2 versus 3.3, 34 versus. 40, 2447 versus 2114, 121 versus 152, respectively. Complications (admission to intensive care unit, pancreatic necrosis with septicemia, large (>6 cm) pseudocyst formation, need for surgical necrosectomy) were less frequent in the PD stent group resulting in a significantly lower overall complication rate (10 % vs 31 %). Mortality rates (0 % vs 4 %) were comparable, reasonably low and without any significant differences. Temporary small-caliber PD stent placement may offer sufficient drainage to reverse the process of ABP. Combined with EST the process results in a significantly less complication rate and better clinical outcome compared with EST alone during the early course of ABP [067].

Laparoendoscopic rendezvous versus preoperative ERCP

Although the ideal management of cholecysto-choledocholi-thiasis is controversial, the 2stage approach [endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy, and common bile duct (CBD) clearance followed by laparoscopic cholecystectomy] remains the standard way of management worldwide. One-stage approach using the so-called laparoendoscopic rendezvous (LERV) technique offers some advantages, mainly by reducing the hospital stay and the risk of post-ERCP pancreatitis. To compare the LERV 1stage approach with the standard 2-stage approach consisting of preoperative ERCP followed by laparoscopic cholecystectomy for the treatment of cholecysto-choledocholithiasis a controlled randomized trial was performed. Patients with cholecysto-choledocholithiasis were randomized either to LERV or to the 2-stage approach. Both elective and emergency cases were included in the study. Primary endpoint was to detect difference in overall hospital stay, whereas secondary endpoints were to detect differences in morbidity (especially post-ERCP pancreatitis) and success of CBD clearance. This was an interim analysis of the first 100 randomized patients. Hospital stay was significantly shorter in the LERV group; median 4 (2-19) days versus 6 (3-22) days. There was no difference in morbidity and success of CBD clearance between the 2 groups. Post-ERCP amylase value was found significantly lower in the LERV group: median 65 (16-1159) versus 91 (30-1846). It was concluded that the interim analysis of the results suggests the superiority of the LERV technique in terms of hospital stay and post-ERCP hyperamylasemia [068].

Acute alcoholic pancreatitis

Alcohol is oxidized to acetaldehyde, which in turn is oxidized to acetate. The aldehyde dehydrogenase 2 gene (ALDH2) is the most important gene responsible for acetaldehyde metabolism. Individuals heterozygous or homozygous for the lys (A or *2) allele at the single nucleotide polymorphism (SNP) glu504lys (rs671) of ALDH2 have greatly reduced ability to metabolize acetaldehyde, which greatly decreases their risk for alcohol dependence. Case-control studies have shown association between this SNP and alcohol dependence as well as alcohol-induced liver disease. However, some studies have produced insignificant results.

Using cumulative data from the past 20 years predominately from Asian populations (from both English and Chinese publications), this meta-analysis sought to examine and update whether the aggregate data provide new evidence of statistical significance for the proposed association. The results (9,678 cases and 7,331 controls from 53 studies) support a strong association of alcohol abuse and dependence, with allelic P value of $3 \times 10(-56)$ and OR of 0.23 under the random effects model. The dominant model (lys-lys + lys-glu vs glu-glu) also showed strong association with P value of $1 \times 10(-44)$ and OR of 0.22). When stricter criteria and various sub-group analyses were applied, the association remained strong (for example, OR 0.23 and P = $2 \times 10(-28)$ for the alcoholic patients with alcoholic liver disease, cirrhosis, or pancreatitis). These findings provide confirmation of the involvement of the human ALDH2 gene in the pathogenesis of AD as well as alcohol-induced medical illnesses in East-Asians [069].

Experimental

Aim of one study was to investigate pancreatic microcirculatory and histopathological changes in rats after chronic ethanol liquid diet feeding. To investigate the influence of chronic alcohol exposition (CAE) on the pancreas, rats were fed with either Lieber-DeCarli (LDC) control diet or LDC alcohol diet for 2, 4, or 6 weeks and received additionally an acute ethanol administration (AEA) for 90 minutes. Intravital microscopy was performed at baseline, 45 minutes, and 90 minutes after starting AEA. Pancreatic perfusion and leukocyte adhesion were assessed, and pancreatic damage was evaluated by histology. Capillary perfusion was reduced in all animals after AEA. After previous CAE, there was a significant increase in leukocyte adhesion compared to control groups. Most importantly, leukocyte adhesions were already increased at baseline after CAE and before the acute bolus was infused. Moreover, only animals that received LDC alcohol diet developed mild histological changes consisting of pancreatic edema and vacuoles, whereas those that received AEA alone did not. Histological changes and cytokine levels correlated with the duration of prior CAE. It was concluded that long-term alcohol intake activates endothelium and sensitizes the pancreas for inflammatory reactions leading to an increased likelihood of a clinically evident episode of acute pancreatitis [070].

Post-ERCP-pancreatitis

Pancreatitis requiring hospitalization is the most common complication of ERCP. Numerous pharmaceutical and procedure related interventions have been studied in attempts to prevent this complication; however, morbidity associated with ERCP remains significant. The most effective methods for preventing post-ERCP pancreatitis are careful patient selection and identification of risk factors prior to procedure. One article reviewed the most recent literature with significant findings pertaining to the prevention of postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Despite several promising reports of pharmacologic agents that have demonstrated the efficacy for prophylaxis against post-ERCP pancreatitis such as nonsteroidal anti-inflammatory drugs and secretin, there are currently no universally accepted agents for use in high-risk patients. The greatest reductions in the incidence of post-ERCP pancreatitis in high-risk patients have been demonstrated through advancements in endoscopic techniques such as pancreatic duct stenting and dye-free guidewire cannulation [071].

Rectal indometacine as prophylaxis

Preliminary research suggests that rectally administered nonsteroidal antiinflammatory drugs may reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). In one multicenter, randomized, placebo-controlled, double-blind clinical trial, we assigned patients at elevated risk for post-ERCP pancreatitis to receive a single dose of rectal indomethacin or placebo immediately after ERCP. Patients were determined to be at high risk on the basis of validated patient- and procedure-related risk factors. The primary outcome was post-ERCP pancreatitis, which was defined as new upper abdominal pain, an elevation in pancreatic enzymes to at least three times the upper limit of the normal range 24 hours after the procedure, and hospitalization for at least 2 nights. A total of 602 patients were enrolled and completed follow-up. The majority of patients (82 %) had a clinical suspicion of sphincter of Oddi dysfunction. Post-ERCP pancreatitis developed in 27 of 295 patients (9 %) in the indomethacin group and in 52 of 307 patients (17 %) in the placebo group, which was a statistically significant difference. Moderate-to-severe pancreatitis developed in 13 patients (4.4 %) in the indomethacin group and in 27 patients (8.8 %) in the placebo group, which also was significantly different. Thus, among patients at high risk for post-ERCP pancreatitis, rectal indomethacin significantly reduced the incidence of the condition [072].

Low dose heparin

One of the most frequent and serious complications of endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis. The aim of this study was to evaluate the preventive effect of low-dose heparin (unfractionated or low-molecular-weight heparin) on post-ERCP pancreatitis (PEP) and its side-effects by a systematic review and meta-analysis of clinical trials. Searching PubMed and EMBASE, up to August 2011, two independent reviewers systematically identified prospective clinical trials detecting the effect of prophylactic low-dose heparin on the incidence of PEP, severe PEP, and post-ERCP hemorrhage complications. Four clinical trials fulfilled our selection criteria, with three prospective randomized and one nonrandomized. A meta-analysis of these clinical trials was then performed. A total of 1438 patients were included. Meta-analysis of these trials indicated that there was no significant association between the use of heparin and the reduction of PEP (RR 0.67, 95 % confidence interval 0.44 to 1.03) and severe PEP (RR 0.62, 95 % confidence interval 0.15 to 2.60). However, low-dose heparin did not increase the incidence of post-ERCP hemorrhage complications. This meta-analysis did not demonstrate a statistically significant benefit of prophylactic heparin use for the prevention of post-ERCP pancreatitis. More multicenter trials involving a larger number of patients are needed to show a possible prevention effect of PEP from heparin and its related compounds [073].

Triglceride-induced acute pancreatitis

A case of hypertriglyceridemia-induced acute pancreatitis that was managed with insulin and heparin was reported. A 39-year-old Hispanic man arrived at the emergency department with complaints of abdominal pain, nausea, and vomiting over one day. A computed tomography scan of the abdomen revealed peripancreatic inflammatory changes surrounding the tail of the pancreas, consistent with pancreatitis. Pertinent laboratory test values on admission were as follows: triglyceride concentration, 5366 mg/dL; total cholesterol concentration, 555 mg/dL; amylase concentration, 131 units/L; lipase concentration, 51 units/L; serum glucose concentration, 253 mg/dL; and serum sodium concentration, 128 mmol/L. The patient was diagnosed with hypertriglyceridemia-induced pancreatitis. On hospital day 1, the patient was given nothing by mouth and received a 1-L bolus dose of 0.9% sodium chloride injection, followed by a continuous infusion of 0.9% sodium chloride injection at a rate of 125 mL/hr. Subcutaneous heparin 5000 units every eight hours, sliding-scale regular insulin, and gemfibrozil 600 mg twice daily were initiated. On hospital day 2, the patient's triglyceride concentration decreased to 2962 mg/dL, and his blood glucose concentration was 147 mg/dL. Subcutaneous insulin detemir 25 units daily was ordered, and sliding-scale insulin was continued. Due to continued elevated triglyceride levels, the patient was transitioned

from subcutaneous insulin to an i.v. insulin infusion at 0.1 unit/kg/hr in addition to an infusion of 5 percent dextrose. On hospital day 5, the patient's triglyceride concentration decreased to 717 mg/dL; the insulin-dextrose infusion was discontinued. The patient was discharged on hospital day 6. A 39-year-old man with pancreatitis caused by severe hypertriglyceridemia was treated with a continuous insulin infusion and subcutaneous heparin [074].

Plasmapheresis

A 10-year-old girl presented with diabetic ketoacidosis, shock, and severe abdominal pain. She was found to have acute pancreatitis and acute kidney injury after shock resuscitation and severe persistent hypertriglyceridemia. The severe hypertriglyceridemia was treated with 1 course of plasmapheresis, which corrected the triglyceride level and was temporally associated with improvement of the abdominal pain and renal dysfunction. Diabetes is known to contribute to an elevated triglyceride level, especially in the setting of an underlying lipid disorder. However, no such disorders were found in this patient. This is the first report of a pediatric patient presenting with the triad of severe hypertriglyceridemia, diabetic ketoacidosis, and pancreatitis treated successfully with plasmapheresis [075].

Experimental

Hyperlipidemia is associated with a variety of pancreatic diseases. However, the underlying pathophysiology and molecular mechanisms between hyperlipidemia and acute pancreatitis remain undefined. Gel electrophoresis and mass spectrometry can be used in proteomic analysis to elucidate these mechanisms. A comparative proteomic analysis was conducted to identify proteins that were altered in pancreases of hyperlipidemic acute necrotic pancreatitis rats compared with those of normal-lipid acute necrotic pancreatitis rats. A comparative proteomic approach using a hyperlipidemic rat model was used. Thirty-nine differentially expressed proteins were significantly changed in pancreatic samples from hyperlipidemic acute necrotic pancreatitis rats. Differentially expressed proteins in hyperlipidemic pancreatitis include pancreatic proteolytic enzymes, such as lipase, amylase, carboxypolypeptidase, and α -1-antiproteinase; endoplasmic reticulum stress-related proteins; and calcium influx-related proteins including protein disulfide isomerase, calreticulin, annexin A, glucose-regulated protein 78, heat shock protein 60, and peroxiredoxin. Other proteins associated with DNA replication and damage repair, apoptosis, cell metabolism, circulatory dysfunction, and signal transduction were identified in hyperlipidemic pancreatitis. It was concluded that hyperlipidemia intensifies acute necrotic pancreatitis through various ways. These enzymes may be putative biomarkers of hyperlipidemic acute necrotic pancreatitis [076].

Outflow obstruction acute pancreatitis

Due to pancreatic hydatid cyst

Hydatid disease is a major health problem worldwide. Primary hydatid disease of the pancreas is very rare and acute pancreatitis secondary to hydatid cyst has rarely been reported. It was reported a case of a 38-year-old man who presented acute pancreatitis. A diagnosis of hydatid cyst of the pancreas, measuring 10 cm, was established by abdominal computed tomography before surgery. The treatment consisted of a distal pancreatectomy. The postoperative period was uneventful. Additionally, a review of the literature regarding case reports of acute pancreatitis due to pancreatic hydatid cyst was presented [077].

IPMN

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a distinct entity characterized by papillary proliferations of mucin-producing epithelial cells with excessive mucin production and cystic dilatation of the pancreatic ducts. The clinical presentation often involves recurrent episodes of pancreatitis associated with the temporal obstruction of the main pancreatic duct caused by the hypersecretion of mucin. We herein describe a case in which the patient repeatedly experienced the occurrence of idiopathic acute pancreatitis in the head of the pancreas over a 9-year period, and who was ultimately was cured by distal pancreatectomy for IPMNs in the pancreatic tail. This case illustrates the potential pitfalls in the diagnosis of IPMNs owing to a discrepancy between the site of pancreatitis and that of the IPMN. The possible mechanisms linking acute pancreatitis with the formation of IPMNs are also reviewed [078].

Anomalous pancreaticobiliary junction

Anomalous pancreaticobiliary junction (APBJ) is the term used to describe anatomical variants of pancreatic and biliary ductal junctional anatomy. Patients have junction of the pancreatic and bile ducts located outside the duodenal wall, forming a long common channel. We report our findings and clinical outcomes in a North American series of patients with APBJ undergoing ERCP. It was reviewed 2,218 ERCP performed on 1,050 patients. Twelve patients (1.1 %) with APBJ were identified (5F, 7M). No patient had an associated choledochocele. Mean age was 53 (range 17-85). A total of 43 ERCP procedures were performed on these 12 patients. All patients experienced passive pancreatography. No patient developed post-ERCP pancreatitis. Only one patient had a history of antecedent pancreatitis. In conclusion, in North American patients undergoing ERCP, 1.1 percent of patients had APBJ. Our study population was predominately Caucasian, male, and in all but one patient lacked a history of prior pancreatitis. No patient developed post-ERCP pancreatitis. This suggests that APBJ may have different clinical manifestations in a North American population when compared to Asian populations [079].

Duodenal diverticula

Juxtapapillary duodenal diverticula (DD), although usually asymptomatic, are occasionally associated with pancreaticobiliary conditions such as recurrent bile duct stones, cholangitis, and pancreatitis. An unusual case of DD associated with a dorsal duct stricture in a patient with recurrent pancreatitis and pancreas divisum is presented along with three additional instances of surgically treated DD and a review of the literature. The role of surgical intervention depends upon the specific nature of the presentation and the anatomical relationship of the diverticulum to the ampullary and pancreaticobiliary ductal system. Operations that divert bile and the food stream from DD are preferred over diverticulectomy [080].

Drug-induced acute pancreatitis

Drugs are thought to be a rare cause for acute pancreatitis; however 525 different drugs are listed in the World Health Organization (WHO) database suspected to cause acute pancreatitis as a side effect. Many of them are widely used to treat highly prevalent diseases. The true incidence is not entirely clear since only few systematic population based studies exist. The majority of the available data are derived from case reports or case control studies. Furthermore, the causality for many of these drugs remains elusive and for only 31 of these 525 dugs a definite causality was established. Definite proof for causality is defined by the WHO classification if symptoms reoccur upon rechallenge.In the actual algorithm the

diagnosis is confirmed if no other cause of acute pancreatitis can be detected, and the patient is taking one of the suspected drugs [081].

Sitagliptin

To report the first postmarketing case of necrotizing pancreatitis in a patient on combination therapy of sitagliptin and exenatide it was described the patient's clinical presentation, laboratory test results, imaging, and autopsy findings. A 76-year-old woman with a history of type 2 diabetes mellitus presented with severe abdominal pain, vomiting, and fever requiring hospital admission. She had been treated with exenatide for 3 years to manage her diabetes mellitus. A few weeks before presentation, sitagliptin was added, presumably to further optimize her glycemic control. Acute pancreatitis was diagnosed during hospital admission. At initial presentation, her serum amylase concentration was 1136 U/L (reference range, 10-130 U/L) and her lipase concentration was greater than 3500 U/L (reference range, 0-75 U/L). In addition, computed tomography of the abdomen and pelvis demonstrated extensive previous cholecystectomy, reported no alcohol consumption, and had a normal lipid profile. Although she had a long-standing history of diabetes mellitus, she had no history of pancreatitis or other risk factors that would have caused her to develop the underlying condition. After initial brief improvement, her symptoms worsened, and despite aggressive care, her clinical state deteriorated and she died. Autopsy findings demonstrated acute necrotizing pancreatitis with complete digestion of the pancreas. It was concluded that considering the temporal relationship of her symptoms to the addition of sitagliptin to her existing exenatide regimen, this case strongly suggests a possible causal link between exenatide or sitagliptin (or the combination of the 2 drugs) and the etiology of pancreatitis in this patient [082].

Hypthermia-induced acute pancreatitis

Therapeutic hypothermia in adult victims who suffer cardiac arrest following drowning has been applied in only a small number of cases. In the last 4 years, it was employed therapeutic hypothermia to decrease hypoxia-induced brain injury in these patients. The purpose of the present study was to report the results of the treatment of these patients. One study investigated the utilisation of therapeutic hypothermia on consecutive patients with cardiac arrest because of drowning between 2005 and 2008. The study was conducted retrospectively, collecting data by reviewing medical records. Hypothermia, with a target temperature of 32-34°C, was induced for 24 h. Neurological outcomes were classified using the cerebral performance categories (CPCs). The primary outcome was neurological function at discharge. Twenty patients were treated with therapeutic hypothermia. Four patients (20%) exhibited a favourable neurological outcome (CPC 1-2). Two patients (10%) remained in a vegetative state at discharge (CPC 4), and 14 patients (70 %) died (CPC 5). The most common complications during therapeutic hypothermia were pancreatitis and rhabdomyolysis. A longer duration of advanced cardiac life support, an absence of motor response to pain after 3 days, an abnormal brain imaging and a lack of cortical response to somatosensory evoked potential were related to an unfavourable outcome (CPC 3-5). The present study did not demonstrate an advantage of therapeutic hypothermia in adult cardiac arrest after drowning compared with previous studies treated with conventional therapy. Further prospective studies are needed to evaluate the effects of therapeutic hypothermia [083].

Dialysis-induced acute pancreatitis

Abdominal pain with a discoloured dialysate in a patient on peritoneal dialysis (PD) is usually attributed to infective peritonitis. Although acute pancreatitis (AP) is not usually a complication of end-stage renal disease, some studies suggest an increased risk especially in patients on PD. It was reported a case of idiopathic AP in a 41-year-old female on PD who presented with abdominal pain, fever, vomiting and a clear dark dialysate. Initial diagnosis of PD-associated infective peritonitis was made but dialysate cultures proved negative. Serum amylase showed a mild rise and computed tomography revealed necrotising pancreatitis. No common risk factors for AP were identified and she was successfully treated with conservative therapy. A literature review was carried out using a PubMed search with the words 'acute pancreatitis and peritoneal dialysis'. The literature search found a total of 94 cases of AP in the setting of PD. In more than a quarter, no cause for AP was found. Serum amylase was normal in 12.8% of episodes. Complications developed in 25 cases, and 28 patients died from the condition. Therefore, AP can be a rare, but serious complication of PD with a high mortality and must be considered in the differential diagnosis of abdominal pain in a PD patient [084].

Vascular complications of pancreatitis

Major vascular complications related to pancreatitis can cause life-threatening hemorrhage and have to be dealt with as an emergency, utilizing a multidisciplinary approach of angiography, endoscopy or surgery. These may occur secondary to direct vascular injuries, which result in the formation of splanchnic pseudoaneurysms, gastrointestinal etiologies such as peptic ulcer disease and gastroesophageal varices, and post-operative bleeding related to pancreatic surgery. In this review article, we discuss the pathophysiologic mechanisms, diagnostic modalities, and treatment of pancreatic vascular complications, with a focus on the role of minimally-invasive interventional therapies such as angioembolization, endovascular stenting, and ultrasound-guided percutaneous thrombin injection in their management [085].

Endovascular stenting

To evaluate the experience with the endovascular treatment of total occlusions of the mesenteric and celiac arteries it was performed a retrospective review of endovascular stenting of 27 nonembolic total occlusions of the superior mesenteric artery (SMA) and celiac artery (CA) between July 2004 and July 2011 (26 patients, 16 females; mean age, 62 ± 13 years). A variety of demographic, lesion-related and procedure-related variables were evaluated for potential impact of technical success and patency. The follow-up protocol included clinical assessment, and color and spectral Doppler evaluation of the stented vessel(s). The clinical presentation was chronic mesenteric ischemia in 12 patients, acute mesenteric vascular syndromes in 10 patients, foregut ischemia/ischemic pancreatitis in three patients, and prior to endovascular repair of aortic aneurysm in one patient. The treated vessel was SMA in 22 procedures, CA in three, and both SMA and CA in one. Technical success was achieved in 23 of the 27 attempted recanalizations (85 %). Three patients who failed the attempt underwent open bypass, and another one underwent retrograde recanalization and stenting of the SMA. Procedure success was only significantly related to patient age <70 years or procedure performance after the year 2006. Notably, the presence of a stump, ostial plaque, extensive vascular calcification, recanalization route (intraluminal vs subintimal), occlusion length, and vessel diameter had no significant impact on procedure success. Traditional duplex criteria proved unreliable in predicting restenosis. Life table analysis of freedom from symptom recurrence showed a primary and assisted rates of 58 and 80 percent at 1 year, and 33 and 60 percent at 2 years, respectively. Clinical

recurrences developed in six patients (four presented with abdominal angina and weight loss, two presented with abdominal catastrophe). There were six access-related complications and no procedural deaths. Four delayed deaths occurred during follow-up (two cardiac causes, two due to abdominal sepsis). It was concluded that endovascular recanalization of mesenteric artery occlusion is both feasible and successful, provided careful planning is used [086].

Diabetes

It is well established that acute pancreatitis often causes diabetes and that a high blood glucose level associated with pancreatitis is a marker of poor prognosis. The aim of one study was to evaluate if diabetes merely reflects the severity of pancreatitis or whether it can also aggravate the progression of this disease in a vicious circle. Reversible acute edematous pancreatitis was induced in untreated and streptozotocin-treated diabetic mice by injection of cerulein. Progression of pancreatitis was studied by immunohistochemistry, ELISA and various other enzyme assays. The production of regenerating islet-derived 3beta was determined by western blot and immunohistochemistry. While cerulein treatment in nondiabetic mice resulted in acute pancreatitis followed by regeneration of the pancreas within 7 days, diabetes aggravated pancreatitis, inhibited the regeneration of the exocrine tissue and led to strong atrophy of the pancreas. The aggravation of pancreatitis by diabetes was characterised by decreased production of the anti-inflammatory protein regenerating isletderived 3beta, increased inflammation, augmented oedema formation and increased cell death during the acute phase of pancreatitis. During the regenerative phase, diabetes augmented inflammation, increased cell death, reduced acinar cell expansion and increased the expansion of duct as well as interstitial cells, resulting in the formation of tubular complexes. Administration of insulin reversed the observed phenotype in diabetic mice. It was concluded that diabetes aggravates acute pancreatitis and suppresses regeneration of the exocrine tissue. Thus, diabetes is not just a concomitant phenomenon of pancreatitis, but can have a fundamental influence on the progression of acute pancreatitis [087].

Coagulation

Systemic inflammation affects hemostasis during severe acute pancreatitis (SAP). A hypercoagulable state occurs more frequently in SAP, which is not fully detected by traditional coagulation testing. The aim of one study was to evaluate the contribution of clot formation and lysis (CloFAL) assay to improve monitoring of global coagulation in patients with SAP. Twenty-five patients with SAP who were treated from 2009 to 2011 were studied. Plasma was collected at the time of admission, and CloFAL was measured using the CloFAL analyzer. The parameters evaluated include coagulation time (CT), fibrinolysis time (FT), and maximum amplitude (MA), from which the accelerating coagulation extent (ACE, MA/CT), accelerating fibrinolytic extent (AFE, MA/FT), and balance level exponent (BLE, ACE/AFE) were calculated. In addition, laboratory values for the traditional coagulation testing were measured. Values were compared to a control group of 20 healthy subjects. The MA, FT, ACE, and BLE values of the CloFAL assay were significantly increased in the SAP group compared to the control group (p\0.05 for all measurements). For the traditional coagulation testing, fibrinogen, plasminogen, and D-dimer levels were higher in patients in the SAP group compared to the control group. The findings using the CloFAL analyzer indicate that the hypercoagulable state was due to increased fibrin generation and invariable fibrinolysis in patients with SAP. CloFAL assay is a simple and useful global coagulation assay to monitor hypercoagulable states during SAP [088].

Parathyroid hormone

Pancreatitis is a common and potentially lethal necro-inflammatory disease with both acute and chronic manifestations. Current evidence suggests that the accumulated damage incurred during repeated bouts of acute pancreatitis (AP) can lead to chronic disease, which is associated with an increased risk of pancreatic cancer. While parathyroid hormone-related protein (PTHrP) exerts multiple effects in normal physiology and disease states, its function in pancreatitis has not been previously addressed. Here we show that PTHrP levels are transiently elevated in a mouse model of cerulein-induced AP. Treatment with alcohol, a risk factor for both AP and chronic pancreatitis (CP), also increases PTHrP levels. These effects of cerulein and ethanol are evident in isolated primary acinar and stellate cells, as well as in the immortalized acinar and stellate cell lines AR42J and irPSCc3, respectively. Ethanol sensitizes acinar and stellate cells to the PTHrP-modulating effects of cerulein. Treatment of acinar cells with PTHrP (1-36) increases expression of the inflammatory mediators interleukin-6 (IL-6) and intracellular adhesion protein (ICAM-1), suggesting a potential autocrine loop. PTHrP also increases apoptosis in AR42J cells. Stellate cells mediate the fibrogenic response associated with pancreatitis; PTHrP (1-36) increases procollagen I and fibronectin mRNA levels in both primary and immortalized stellate cells. The effects of cerulein and ethanol on levels of IL-6 and procollagen I are suppressed by the PTH1R antagonist, PTHrP (7-34). Together these studies identify PTHrP as a potential mediator of the inflammatory and fibrogenic responses associated with alcoholic pancreatitis [089].

In Wegener's granulomatosis

Wegener's granulomatosis is a systemic vasculitis with prominent involvement of the respiratory tract and kidney. There are 10 patients with Wegener's granulomatosis in the literature who were documented as acute pancreatitis. It was presented two new cases with Wegener's granulomatosis presenting with acute pancreatitis and pancreatic pseudocyst. Endosonography-guided drainage of the pancreatic pseudocyst led to rapid clinical improvement. Pancreatic pseudocyst in Wegener's granulomatosis to be managed by endosonography-guided cyst drainage. The safety of endosonography-guided pancreatic pseudocyst drainage and the clinical features of the previous Wegener's granulomatosis cases with acute pancreatitis are discussed [090].

Schnitzler's syndrome

Schnitzler's syndrome is a rare inflammatory disease of unknown origin characterized by chronic urticaria and monoclonal gammopathy (usually IgM) associated with at least two of the following components: fever, arthralgia or arthritis, bone pain, hepato- and/or splenomegaly, lymphadenopathy, elevated erythrocyte sedimentation rate, leukocytosis, and/or abnormal findings on bone morphological investigations. To date, about 100 cases have been described with only 4 being reported in the USA. The mean time to diagnosis from the onset of disease is 5.4 years, given the varied symptoms with which patients may present. The pathogenesis of Schnitzler's syndrome remains unknown but likely involves dysregulation of the IL-1 pathway. It was described a 48-year-old woman with a monoclonal IgM gammopathy and a 3-year history of chronic pruritic urticarial dermatosis, unexplained fevers, chronic polyarthritis, lymphadenopathy, leukocytosis, hepatomegaly, and weight loss. She also had a history of chronic pancreatitis as well as a family history of recurrent pancreatitis. The diagnosis of Schnitzler's syndrome was made, and she was successfully treated with the IL-1 receptor antagonist, anakinra [091].

Disconnected pancreatic duct syndrome

After acute necrotizing pancreatitis (ANP), a pancreatic fistula may occur from disconnected pancreatic duct syndrome (DPDS) where a segment of the pancreas is no longer in continuity with the main pancreatic duct. Between 2002 and 2011, patients treated for DPDS in the setting of endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopanreatography (MRCP) documented main pancreatic duct disruption with Roux-Y pancreatic fistula tract-jejunostomy. In all, seven patients with DPDS were treated. The median age was 62 years (range 49-78) and five were men. The cause of ANP was gallstones (2), alcohol (1), ERCP (1) and idiopathic (3). Pancreatic necrosectomy was done in six patients. Time from onset of pancreatitis to fistula drainage was 270 days (164-365). Pancreatic fistulae arose from DPDS in the head/neck (4) and body/tail (3). Patients had a median fistula output of 140 ml (100-200) per day before surgery. The median operative time was 142 min (75-367) and estimated blood loss was 150 ml (25 to 500). Patients began an oral diet on post-operative day 4 (3-6) and were hospitalized for a median of 7 days (5-12). The median follow-up was 264 days (29-740). Subsequently, one patient required a distal pancreatectomy. After surgery, three patients required oral hypoglycaemics. No patient developed pancreatic exocrine insufficiency. It was concluded that internal surgical drainage using Roux-en-Y pancreatic fistula tract-jejunostomy is a safe and definitive treatment for patients with DPDS [092].

Early enteral feeding

One study aimed to determine the noninferiority of early enteral feeding through nasogastric (NG) compared to nasojejunal (NJ) route on infectious complications in patients with severe acute pancreatitis (SAP). Patients with SAP were fed via NG (candidate) or NJ (comparative) route. The primary outcome was the occurrence of any infectious complication in blood, pancreatic tissue, bile, or tracheal aspirate. Secondary end points were pain in refeeding, duration of hospital stay, intestinal permeability assessed by lactulose/mannitol excretion, and endotoxemia assessed by endotoxin core antibody types immunoglobulin G and M. Seventy-eight patients were randomized to feeding by either the NG or the NJ route. During the hospital stay, the presence of any infectious complication in the NG and NJ groups was 23 and 36 percent (significantly different), respectively. The effect size of the difference of infectious complications was -13 percent. The upper limit of the 95 percent confidence interval was 4.0 and was within the 5 percent limit set for noninferiority. The value of 8.0 for the number needed to treat implies that 8 patients should be treated with NG compared with the NJ group to prevent 1 patient from any of the infectious complications. It was concluded that early enteral feeding through NG was not inferior to NJ in patients with SAP. Infectious complications were within the noninferiority limit. Pain in refeeding, intestinal permeability, and endotoxemia were comparable in both groups [093].

Treatment with daptomycin

Enterococci are a frequent cause of nosocomial infections in gastroenterology. The increase of Enterococcus faecium infections with development of resistance to gentamicin and vancomycin as well as possible linezolid resistance require alternative antibiotic therapies. Study data show that daptomycin, a highly bactericidal antibiotic is effective in enterococcal infections. However, in Germany daptomycin is so far only approved for the treatment of complicated skin and soft tissue infections, bacteremia and infective endocarditis caused by Staphylococcus aureus. In the Department of Internal Medicine I, University Hospital Halle (Saale) from May 2 009 to April 2 010 all gastroenterological patients with evidence of invasive enterococcal infection received intravenous daptomycin treatment at inclusion in the European Cubicin® Outcomes Registry and Experience (EU-CORE). Gastroenterological

diseases treated were necrotising pancreatitis, infected pancreatic pseudocysts, abscesses, obstructive cholangitis and sepsis. The clinical outcome was retrospectively detected by protocol-defined criteria. A total of 13 patients (8 male, 5 female, median age 59 years) with microbiologically assured enterococcal infections ($10 \times E$. faecium, including $1 \times VRE$, $6 \times E$. faecalis, including double infections) were treated with intravenous daptomycin (6 mg per kg body weight). In the presence of polymicrobial infections ($10 \circ 13$ patients), an additional anti-infective therapy was initiated according to sensitivity testing. Concomitantly a direct focus approach with stenting, puncture or drainage was performed. The clinical cure rate was 92 percent ($12 \circ 13$ patients). One patient died from a non-surgically uncontrollable malignancy (Klatskin tumour Bismuth IIIb). There were no adverse events. These results allow us to conclude that antibiotic therapy with daptomycin in invasive or bacteraemic enterococcal infections leads to high cure rates (up to 90 % and more) when concomitant and adequate focus relief is performed. Larger clinical studies to obtain an extended drug approval are desirable [094].

Antibiotics

To investigate the role of prophylactic antibiotics in the reduction of mortality of severe acute pancreatitis (SAP) patients, which is highly questioned by more and more randomized controlled trials (RCTs) and meta-analyses. An updated meta-analysis was performed. RCTs comparing prophylactic antibiotics for SAP with control or placebo were included for meta-analysis. The mortality outcomes were pooled for estimation, and re-pooled estimation was performed by the sensitivity analysis of an ideal large-scale RCT. Currently available 11 RCTs were included. Subgroup analysis showed that there was significant reduction of mortality rate in the period before 2000, while no significant reduction in the period from 2000. Funnel plot indicated that there might be apparent publication bias in the period before 2000. Sensitivity analysis showed that the RR of mortality rate ranged from 0.77 to 1.00 with a relatively narrow confidence interval. However, the number needed to treat having a minor lower limit of the range (7-5096 patients) implied that certain SAP patients could still potentially prevent death by antibiotic prophylaxis. Current evidences do not support prophylactic antibiotics as a routine treatment for SAP [095].

Peripancreatic fluid collections

Pancreatitis associated with the extension of a pancreatic collection, pseudocyst or abscess into the groin is a rare phenomenon with few reports in the English literature. Nevertheless, it remains a clinically important differential diagnosis as it may be mistaken for more common pathologies in the groin and with a subsequent unnecessary surgical intervention. A case of this rare complication of pancreatitis was reported, together with a review of the literature [096].

Pancreatic necrosis

To learn the clinical outcome of percutaneous catheter drainage (PCD) for patients with infective pancreatic necrosis and the possible influencing factors a retrospective review of medical records of patients with infective pancreatic necrosis who received PCD as the first choice for treatment in the recent 2 years. The patients were divided into 2 groups: PCD success group and PCD alteration group. Characteristics, complications, and PCD process were compared. In this study, 19 of 34 patients were cured by PCD alone (56 %), whereas open necrosectomy were needed for 15 patients (44 %). Between these 2 groups, most baseline and clinical characteristics did not show any statistical difference, including the

number and size of catheter used and the bacterial culture result. The PCD alteration group had higher mean computed tomographic density and larger distribution range of infected pancreatic necrosis $(4.5 \pm 1.4 \text{ vs } 5.9 \pm 1.6)$ than the PCD success group. The logistic regression analysis revealed the same facts. The mean computed tomographic density and distribution range of infective pancreatic necrosis could significantly influence the success rate of PCD; higher values of them indicate less appropriate for PCD; thus, it should be considered seriously before the treatment decision [097].

Diagnosis

Labeled leukocyte scintigraphy has been used as an indicator of pancreatic necrosis in patients with acute pancreatitis and proposed for the detection of infection in peripancreatic fluid collections. The authors present a PET/CT scan showing abnormal uptake of 18F-Fluorodeoxyglucose-labeled autologous leukocytes in a pancreatic pseudocyst, from which aspirated fluid subsequently showed growth of Pseudomonas aeruginosa [098].

Interventions

Currently, necrosectomy remains the cornerstone in the surgical treatment of infected pancreatic necrosis and in selected cases of sterile necrotizing pancreatitis. Following necrosectomy, continuous closed lavage is recommended by many authors, while closed abdominal packing /drainage and repeated planned necrosectomies- commonly using the zipper technique-are also acceptable alternative strategies. Open abdomen (laparostomy) is rarely indicated in carefully selected cases (typically in abdominal compartment syndrome associated with necrotizing AP). During the last decade, minimally invasive techniques (including percutaneous drainage, retroperitoneal endoscopic approach, transgastric endoscopic approach etc) have been extensively studied by some groups not only in the management of pancreatic abscesses and / or pseudocysts, but also as primary methods of treatment of necrotizing AP. Results have been impressive, but experience currently is limited to only a few centers around the world [099].

Endoscopic transgastric versus surgical necrosectomy

Most patients with infected necrotizing pancreatitis require necrosectomy. Surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, may reduce the proinflammatory response and reduce complications. It was compared the proinflammatory response and clinical outcome of endoscopic transgastric and surgical necrosectomy in a randomized controlled assessorblinded clinical trial in 3 academic hospitals and 1 regional teaching hospital in The Netherlands between 2008 and 2010. Patients had signs of infected necrotizing pancreatitis and an indication for intervention. It was a random allocation to endoscopic transgastric or surgical necrosectomy. Endoscopic necrosectomy consisted of transgastric puncture, balloon dilatation, retroperitoneal drainage, and necrosectomy. Surgical necrosectomy consisted of video-assisted retroperitoneal debridement or, if not feasible, laparotomy. The primary end point was the postprocedural proinflammatory response as measured by serum interleukin 6 (IL-6) levels. Secondary clinical end points included a predefined composite end point of major complications (new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, or pancreatic fistula) or death. It was randomized 22 patients, 2 of whom did not undergo necrosectomy following percutaneous catheter drainage and could not be analyzed for the primary end point. Endoscopic transgastric necrosectomy reduced the postprocedural IL-6 levels compared with surgical necrosectomy. The composite clinical end point occurred less often after endoscopic necrosectomy (20 % vs 80 %; risk difference). Endoscopic necrosectomy did not cause new-onset multiple organ failure (0 % vs 50 %) and

reduced the number of pancreatic fistulas (10 % vs 70 %). It was concluded that in patients with infected necrotizing pancreatitis, endoscopic necrosectomy reduced the proinflammatory response as well as the composite clinical end point compared with surgical necrosectomy [100].

Step-up strategy

In patients with infected necrotising pancreatitis there is a significant risk (40 %) of complications and mortality with the surgical step-up approach. This approach consists of percutaneous retroperitoneal drainage, if necessary followed by video-assisted retroperitoneal débridement. An alternative treatment is an endoscopic step-up approach consisting of endoscopic transluminal drainage, if necessary followed by endoscopic transluminal necrosectomy. The Dutch Pancreatitis Study Group has recently started the nationwide randomized TENSION-trial, in which in 98 patients the endoscopic step-up approach is compared with the surgical method. The primary endpoint is a composite of mortality and major morbidity (new onset organ failure, bleeding, perforation of a hollow organ or incisional hernia for which intervention is needed) [101].

EUS-guided endoscopic necrosectomy

Findings have shown endoscopic necrosectomy to be beneficial for patients with symptomatic pancreatic necrosis accessible for an endoscopic approach. The available studies show that endoscopic necrosectomy requires a multitude of subsequent procedures including repeat irrigation for removal of the necrotic material. This study aimed to investigate the need for additional irrigation in patients with necrotizing pancreatitis treated by endoscopic necrosectomy. The study enrolled 35 consecutive patients (27 men) with a median age of 59 years who had pancreatic necrosis treated with endoscopic necrosectomy. Endoscopic ultrasound-guided internal drainage and consecutive endoscopic necrosectomy was combined with interval multistenting of the cavity. Neither endoscopic nor external irrigation was part of the procedure. An average of 6.2 endoscopy sessions per patient was needed for access, necrosectomy, and stent management. The in-hospital mortality rate was 6 percent (2/35), including one procedure-related death resulting from postinterventional aspiration. The immediate morbidity rate was 9 percent (3/35). It was possible to achieve clinical remission for all the surviving patients with no additional surgery needed for management of the necroses. The median follow-up period was 23 months. It was concluded that neither endoscopic nor external flushing is needed for successful endoscopic treatment of symptomatic necroses. Even without irrigation, the outcome for patients treated with endoscopic necrosectomy is comparable to that described in the published data [102].

To determine the immediate and long-term results of endoscopic drainage and necrosectomy for symptomatic pancreatic fluid collections the data of 80 patients with symptomatic pancreatic fluid collections (mean diameter: 12 cm, range 3-20; pseudocysts: 24/80, abscess: 20/80, infected walled-off necrosis: 36/80) referred for endoscopic management from 1997 to 2008 were analyzed retrospectively. Endoscopic drainage techniques included endoscopic ultrasound (EUS)-guided aspiration (2/80), EUS-guided transenteric drainage (70/80) and non-EUS-guided drainage across a spontaneous transenteric fistula (8/80). Endoscopic necrosectomy was carried out in 49/80 (abscesses: 14/20; infected necrosis: 35/36). Procedural complications were bleeding (12/80), perforation (7/80), portal air embolism (1/80) and Ogilvie Syndrome (1/80). Initial technical success was achieved in 78/80 (98 %) and clinical resolution of the collections was achieved endoscopically in 67/80 (84 %), with surgery required in 13/80 (perforation: four; endoscopically inaccessible areas: two; inadequate drainage: seven). Within 6 months five patients required surgery due to recurrent fluid collections; over a mean follow up of 31 months, surgery was required in four more patients due to recurrent collections as a consequence of underlying pancreatic duct

abnormalities that could not be treated endoscopically. The long-term success of endoscopic treatment was 58/80 (73 %). Endoscopic drainage of symptomatic pancreatic fluid collections is safe and effective, with excellent immediate and long-term results. Endoscopic necrosectomy has a risk of serious complications. The underlying pancreatic duct abnormalities must be addressed to prevent recurrence of fluid collections [103].

Retroperitoneal laparoscopic necrosectomy

Infected pancreatic necrosis is a life-threatening complication of acute pancreatitis that has been traditionally managed with open surgical debridement. Over the last decade, minimally invasive techniques have been increasingly used for the treatment of infected pancreatic necrosis and their results are encouraging. Percutaneous retroperitoneal pancreatic necrosectomy is one of the minimally invasive approaches used for debridement of pancreatic necrosectomy using a single-port access [104].

Late sequelae

After surviving an episode of acute necrotizing pancreatitis (ANP), a variety of late sequelae develop and require nonoperative or operative interventions. Persistent pancreatic fistula, fluid collections, recurrent pancreatitis, sepsis, pain, and intolerance of po intake are seen. It was maintained records for all patients hospitalized from 1993 through 2010 with a diagnosis of ANP. Once discharged from hospital, patients were managed with routine clinic follow-up at close intervals and later at 6-month intervals. Using ERCP or magnetic resonance cholangiopancreatography, all patients' pancreatic ducts were classified as type I (normal), type II (stricture), or type III (disconnected). Patients were monitored for the complications mentioned. Operations performed >8 weeks after the initial episode of ANP were defined as operative mortality, late and evaluated for morbidity. success in resolving symptoms/collections, and length of stay. One hundred and ninety-seven patients with ANP were included. Seventy-one late operations were performed (59 drainage procedures/12 resections). Operative mortality was 1%, morbidity was 19%, and mean length of stay was 6 ± 6 days. Poor po intake was seen in 80 percent of operated patients and total parenteral nutrition dependence in 42 percent. Duct type correlated with pancreatic debridement, persistent fluid collection/fistula, pain, po intake intolerance, and late operation. Late operation successfully resolved symptoms and/or fluid collections in 96 percent. Recurrent pancreatitis was improved in 87 percent and eliminated in 78 percent. Patients who require late operation after surviving an episode of ANP are more likely to have sustained ductal injuries and are likely to require operation for either pain or for inability to tolerate po intake. Operation can be performed safely with a low mortality [105].

Pulmonary embolism

Vascular complications of pancreatitis are a major cause of morbidity and mortality and are related to haemorrhage resulting from arterial erosion or pseudoaneurysms, ischaemic complications (either "local" or related to remote vascular events) and venous or arterial complications – specifically splanchnic thrombosis and associated varices. Pulmonary embolism (PE) is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream (embolism). Usually this is due to embolism of a thrombus (blood clot) from the deep veins in the legs, a process termed venous thromboembolism. A small proportion is due to the embolization of air, fat, talc in drugs of intravenous drug abusers or amniotic fluid. Untreated, PE has a mortality rate of approximately 30 percent. There is increasing evidence that endothelial dysfunction is one of the critical pathophysiologic manifestations in patients with

severe form of acute pancreatitis. Acute pancreatitis is an inflammatory disease characterized by local tissue injury which can trigger a systemic inflammatory response. Vascular complications of pancreatitis are a major cause of morbidity and mortality. Pulmonary embolism in acute pancreatitis has been reported to be very rare. It was reported a case of pulmonary embolism with acute pancreatitis. A 38-year-old woman had been diagnosed with acute pancreatitis in local hospital. A computed tomographic scan of the abdomen revealed pancreatitis. Subsequent computer tomography angiography of chest revealed pulmonary embolism (both pulmonary arteries, left pulmonary artery and branch of right pulmonary artery) [106].

Abdominal compartment syndrome

The incidence of intraabdominal hypertension or abdominal compartment syndrome, as the more severe form is called, is relatively high in patients with severe acute pancreatitis, and therefore more attention is needed to the topic. If conservative treatment fails, immediate surgical decompression is indicated. The most commonly used operation is a full thickness median laparotomy, but a transversal laparotomy may also be effective. Although subcutaneous linea alba, or bilateral anterior rectus fasciotomy is safe and effective, decompressive laparotomy is indicated in failure of these methods. The open abdomen therapy is not advised due to high morbidity. Primary closure of the abdomen is preferable [107].

Nutrition

According to recent studies, intravenously administered glutamine with total parenteral nutrition may be beneficial in the prevention of infectious complications and may reduce mortality rate. However, it has not been investigated yet, whether i.v. glutamine is able to achieve the same effect with early enteral nutrition as well. The objective of one prospective randomized double-blind study was to explore the effects of intravenously administered glutamine with early nasojejunal nutrition in severe acute pancreatitis. Forty-five patients with severe acute pancreatitis (with a Glasgow score at least 3 and/or a CRP level above 150 mg/mL on admission) were randomized into two groups. Group Glutamine (n=24) was given 0.5 g/kg/day glutamine intravenously, while the control group (n=21) received normal amino acid solution in the same quantity for 7 days. Nasojejunal nutrition was introduced 48 hours after admission in case of all patients, and their management was the same in every other aspect, too. The primary end-points of the study were the rate of pancreas-specific infectious complications and organ failure, and the secondary end-points were the necessity for radiological and surgical interventions, length of hospital stay and mortality rate. In group Glutamine, infected acute peripancreatic fluid collections (APFC) were detected in 4 patients, 2 patients had post-necrotic pancreatic/peripancreatic fluid collections (PNPFC), 2 patients had infected pseudocysts and 2 patients had walled-off pancreatic necrosis (WOPN). Ten patients were cured by ultrasound assisted puncture or drainage successfully. No surgical intervention was necessary. In the control group, 4 patients had infected APFC, 2 patients had infected PNPFC, infected pseudocysts and infected WOPN were diagnosed in 3 cases. Radiological intervention was effective in 9 cases, but 3 patients needed surgery. Three patients died of multi-organ failure, thus the mortality rate of the control group was 14 percent, while the mortality rate of the Glutamine group was zero. The mean hospital stay of the Glutamine group was 11 days, which is significantly shorter than the mean hospital stay of the control group, which was 16 days The results of the Glutamine group are better in every end-points, however, statistically significant difference was detected in one parameter only, the length of hospital stay [108].
Case reports

Dyspareunia

Pancreatic pseudocyst is a complication of acute pancreatitis and it usually manifests with abdominal pain. It was reported a case of a 45-year-old man with a history of acute pancreatitis who presented with abdominal pain, dyspareunia, and a palpable inguinal mass. Computed tomography scan revealed a large loculated pseudocyst that dissected through the pelvic cavity towards the inguinal canal, compressing pelvic and inguinal structures. When a patient with a history of pancreatitis develops an inguinal mass, a dissecting pancreatic pseudocyst should be suspected [109].

Cannabis and acute pancreatitis

Drugs of all types are related to the etiology of pancreatitis in approximately 2 percent of cases. However, there have been very few reports of acute pancreatitis associated with cannabis use in the general population. One report is involved a 22-year-old North African man who presented to our emergency department with transfixiant epigastric abdominal pain, nausea and vomiting. The patient denied any past or familial medical history, was taking no medications chronically and had no history of trauma. The patient admitted to smoke one pack of cigarettes a day and occasional cannabis use, and no alcohol consumption. Biological and morphological explorations found Balthazar grade-A acute pancreatitis with no biliary dilatation or obstruction. The etiological workup was normal and, on repeat questioning, the patient admitted to being a regular and excessive user of cannabis, and to having done so 2 days before the abdominal pain. The use of cannabis is frequently seen worldwide and even in North Africa, and regular users, especially young adults, should be informed of the risk of this possible cannabis-induced pancreatic disease. This case should also be borne in mind, although the association of cannabis with pancreatitis is problematic because of the difficulty in monitoring cannabinoids in the body and the illegality of cannabis use and, consequently, getting patients to admit to using it [110].

Panniculitis

It was reported an unusual history of pain in a young patient in the intensive care unit. A 33 year-old alcoholic male with acute pancreatitis had generalized intense pain and developed erythema on the lower truncus and the lower extremities. Treatment with different antibiotics, antihistamines and topical potent steroid cream were all ineffective. A biopsy showed necrotic adipocytes characteristic for pancreatic panniculitis. It was suggest that pancreatic panniculitis should be considered in patients with erythema, pain and known pancreatic disease [111].

Experimental

Impact of age

The severity and mortality rates of acute pancreatitis (AP) are significantly elevated in the elderly population. However, due to a lack of appropriate animal models, the underlying mechanisms for this age-dependent vulnerability remain largely unknown. The purpose of one study was to characterize a murine model of AP, which displays age-associated severity, and to use this model to identify pathophysiologies that are distinctive of the aged with AP. AP was induced in young (4-5 months), middle-aged (12-13 months), and aged (23-25 months) C57BL/6 mice by repeated injection of caerulein, a homologue of the

gastrointestinal hormone cholecystokinin. Approximately 10% of aged mice died during AP, while young and middle-aged mice showed no mortality. Although both young and aged mice exhibited early signs of edema and inflammation in the pancreas, kidney, and lung, young mice showed signs of recovery within 24 h, while aged mice exhibited increasingly severe tissue damage and cell death. There was a significant age-dependent increase in pancreatic neutrophil activation and systemic inflammation as assessed by pancreatic myeloperoxidase and plasma interleukin-6 (IL-6) concentration, respectively. Importantly, aged but not young mice with AP showed significantly elevated thrombosis in the lung and kidney as well as a marked increase in plasma concentration of plasminogen activator inhibitor-1 (PAI-1), a primary inhibitor of the fibrinolytic system. These results demonstrate that aging is associated with increased severity of AP characterized by augmented and prolonged pancreatic inflammation and the presence of multiple extra-pancreatic sequelae including thrombosis [112].

Infliximab

To investigate the synergistic activity of infliximab to the therapeutic effectiveness of octreotide in a rat model of acute necrotizing pancreatitis (ANP) 40Sprague-Dawley rats were randomly divided into sham-operated group (SO), ANP group (ANP), octreotide group (OG), infliximab group (IG), and combination group (CG) (n=8 in each group). The ANP model was induced by biliopancreatic duct injection with 4.5 percent of sodium taurocholate solution. Rats of the OG, IG, and CG were given a tail vein injection of octreotide (10 microg/kg), infliximab (8 mg/kg), and infliximab (8 mg/kg), respectively, combined with octreotide (10 microg/kg) at 6 hours after modeling. All rats in each group were killed at 24 hours after modeling. Serum biochemical indicator and partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) of rats were determined. Pathological severity score of organs were evaluated. The serum biochemical indicator and organs' pathology score of OG, IG, and CG were obviously lower than those in the ANP group, and those in the CG were the lowest. The PaO₂/FiO₂ levels in the OG, IG, and CG were significantly higher than that in the ANP group. It was concluded that Infliximab could significantly lower the serum biochemical indicator, improve organs' function, and enhance the therapeutic effectiveness of octreotide on ANP [113].

CHRONIC PANCREATITIS

Epidemiology

In Asia

Chronic pancreatitis (CP) is widely prevalent in Asian countries much more so in India and Japan. The phenotype of CP is somewhat similar to that reported from western countries. The prevalent types of CP are mainly idiopathic and alcohol related. Current evidence suggests that the term "tropical pancreatitis" used for idiopathic CP from India is a misnomer. Gallstones' association with CP reported from China remains controversial. There has been ample evidence that mutations in the SPNIK1 and CFTR genes are strongly associated with idiopathic CP in patients from different ethnic backgrounds. Oxidative stress is important in the pathophysiology and antioxidants have been shown to result in significant pain relief with CP. Home-made balanced diet is effective for treating malnutrition in patients with CP. Endoscopic therapy combined with ESWL may provide significant relief in patients with pancreatic ductal calculi/stricture. Surgery is quite effective in CP and may be better than endotherapy [114].

Genetics

With novel genetic technologies available, there is a paradigm shift in the way that risk assessments, diagnoses, and therapies for genetic susceptibility syndromes are addressed. Hereditary pancreatitis is among these conditions, for which genetic counseling and next generation sequencing, help families better understand, cope with and live healthier lives. Identifying a genetic etiology to a condition formally believed to be solely environmentally induced can alter the path for treatment for many patients. This finding introduces the concept of gene-environment interactions in human disease and the relationship between genetic predisposition and exposure risk in disease development. The genetic counseling process is complex with medical explanations, psychosocial issues relating to coping with diagnosis, potential future health problems, recurrence risks and family planning. These sometimes difficult conversations can be facilitated by a genetic counselor as a member of the multidisciplinary team. One chapter addresses the intricate medical and psychosocial issues that can arise in the setting of treating patients with hereditary pancreatitis [115].

Mismatch excision repair (MMR)

Pancreatic cancer is characterized by a variety of molecular alterations. Mismatch excision repair (MMR) is a DNA repair system that eliminates mismatched base pairs and it plays an important role in the maintaining of genomic integrity. The aim of the study was to assess the role of several MMR genes in the diagnosis of pancreatic cancer in samples collected by EUS-FNA procedure. The prospective study included 44 consecutive patients with pancreatic cancer (n=24) and chronic pseudotumoral pancreatitis (n=20). EUS-FNA was performed in all the patients. Gene analysis was performed by extracting the mRNA and by determining the expression of DNA repair genes (MLH1, MLH3, MSH6) using a standard algorithm. Total RNA was successfully isolated from all the EUS-FNA pancreatic samples. We analyzed ROC curves to assess the significance of determining the expression of analyzed genes in EUS-FNA samples, obtaining a cutoff value of 476621mRNA copies/mL for MSH6, and sensitivity and specificity of 75 percent and 100 percent, respectively. For MLH1 and MLH3, sensitivity and specificity were only satisfactory (65 % and 76 %, and 75 % and 64 %, respectively). The quality and amount of cellular sampling using pancreatic EUS-FNA allow the extraction of sufficient quantities of RNA to perform qRT-PCR analysis. The use of MMR genes for the

differentiation between pseudotumoral chronic pancreatitis and pancreatic cancer using a minimally invasive sampling technique could be a promising technique [116].

Proteomic analysis

Chronic pancreatitis is characterized by inflammation, fibrosis, pain, and loss of exocrine function of the pancreas. We aimed to identify differentially expressed proteins in the ePFTcollected pancreatic fluid from individuals with chronic pancreatitis (CP; n=9) and controls with chronic abdominal pain not associated with the pancreas (NP; n=9). Using GeLC-MS/MS techniques, we identified a total of 1391 different proteins in 18 pancreatic fluid samples. Of these proteins, 257 and 413 were identified exclusively in the control and chronic pancreatitis cohorts, respectively, and 721 were identified in both cohorts. Spectral counting and statistical analysis thereof revealed an additional 38 and 77 proteins that were up- or down-regulated, respectively, in the pancreatic fluid from individuals with chronic pancreatitis. As expected, gene ontology analysis illustrated that the largest percentage of differentially regulated proteins was secreted/extracellular in origin. In addition, proteins that were down-regulated with statistical significance in the chronic pancreatitis cohort were determined to have biological function of proteases, corresponding to the canonical pancreatic insufficiency associated with chronic pancreatitis. Proteins enriched in the pancreatic fluid of chronic pancreatitis patients had roles in fibrosis, inflammation, and pain, whereas digestive enzymes were significantly less abundant. The workflow provided a mass spectrometry-based approach for the further study of the pancreatic fluid proteome, which may lead to the discovery potential biomarkers of chronic pancreatitis [117].

Intrapancreatic blood flow

It was aimed to compare perfusion computed tomography (CTP) characteristics of the normal pancreas with those of chronic pancreatitis (CP) and to examine the possibility of evaluating pancreatic exocrine function with CTP. Thirty-two patients (control group, n=18; CP group, n=14) who completed the whole pancreas CT perfusion examination with 256slice CT were studied. Four parameters, including perfusion (PF), peak enhancement intensity (PEI), time-to-peak (TTP), and blood volume (BV), were measured and compared between the control and CP groups, and between patients with and without exocrine pancreatic insufficiency (EPI) in the CP group. Pancreatic exocrine function was determined via serum trypsinogen. There was no significant difference between the distribution of PF, PEI, and BV in different pancreas regions, namely, the head, body, and tail. PF, PEI, and BV of the CP group. A significant decrease of PF, PEI, and BV and increase of TTP were observed in patients with EPI than in patients without EPI. Perfusion CT is an appropriate imaging technique to diagnose CP and may be useful as a screening test to rule out early EPI [118].

In liver cirrhosis

It was utilized 320-detector row CT in perfusion CT of multiple abdominal organs and to compare the tissue perfusion between patients with and without liver cirrhosis. The study included 21 patients with cirrhosis and 20 without cirrhosis. The 320-detector row CT scanner enabled multi-organ perfusion CT without requiring the scanner table to be moved. Perfusion was calculated using the maximum slope model for the aorta, the portal vein, the right and left lobes of the liver, the head and body of the pancreas, the spleen, and the corpus and antrum of the stomach. Perfusion in each organ of patients with and without cirrhosis was compared. Portal venous perfusion of the right and left lobes of the liver in

patients with cirrhosis (117 and 100 mL/min/100 mL, respectively) was significantly less than that in patients without cirrhosis (213 and 174 mL/min/100 mL, respectively). Arterial perfusion of the spleen (111 mL/min/100m) and the body of the pancreas (112 mL min/100 mL) in patients with cirrhosis was also significantly decreased compared with that in patients without cirrhosis (body of pancreas 133 mL/min/100mL). The results of the perfusion CT suggest that arterial perfusion of the spleen and the body of the pancreas, as well as portal perfusion of the liver, in cirrhotic patients was decreased compared with that in non-cirrhotic patients [119].

Focal pancreatitis

Mass-forming focal pancreatitis (FP) may mimic pancreatic cancer (PC) on magnetic resonance (MR) imaging, and the preoperative differential diagnosis is often difficult. Recently, the usefulness of diffusion-weighted imaging (DWI) in the diagnosis of pancreatic cancer has been reported in several studies. To investigate if apparent diffusion coefficient (ADC) measurements based on diffusion-weighted echo-planar imaging (DW-EPI) may distinguish between normal pancreas parenchyma, mass-forming focal pancreatitis, and pancreas carcinoma MRI was performed on 64 patients: 24 with pancreas carcinoma (PC), 20 with mass-forming focal pancreatitis (FP), three patients with other focal pancreatic disease as well as 17 controls without any known pancreatic disease. Diffusion-weighted sequence with ADC maps and T2-weighted sequence for anatomical information was performed. Apparent diffusion coefficient (ADC) maps were automatically created and analyzed using a dedicated user interface. In the group with pancreas disease the abnormal parenchyma was detected by using T1- and T2-weighted images and the region of interest (ROI) was transferred exactly to the ADC map and the coefficients were registered. In the control group the ROI was set to the head of the pancreas followed by a similar registration of the ADCs. ADC values for mass-forming FP and PC differed significantly from ADC values for normal pancreas parenchyma. Mean ADC values for mass-forming FP were 0.69 ± 0.18 × 10^{-3} mm²/s. ADC values for PC were 0.78 ± 0.11 × 10^{-3} mm²/s, compared to ADC values of $0.17 \pm 0.06 \times 10^{-3}$ mm²/s in the control group. However there was no significant difference in ADCs between PC and mass-forming FP. ADC measurements clearly differentiated between normal pancreatic tissue and abnormal pancreas parenchyma (PC and mass-forming FP). However there is an overlap in values of PC and mass-forming FP, with the consequent problem of their correct identification [120].

Pancreatic function in diabetes

Decreased function of the exocrine pancreas is frequent in patients with diabetes. The aim of one study was to investigate clinical correlates of pancreatic exocrine failure in patients with diabetes. It was investigated exocrine function by assaying both elastase-1 concentration and chymotrypsin activity in 667 patients. It was conducted separate analysis on patients with type 1 diabetes and patients with type 2 diabetes. Patients were separated into three groups according to whether both elastase-1 concentration and chymotrypsin activity were normal, or one or both were altered. A total of 667 consecutive patients were analysed, including 195 with type 1 and 472 with type 2 diabetes. Elastase-1 concentration was <200 microg/g in 23 percent of the patients. Chymotrypsin activity was <6 U/g in 26 percent of the patients elastase-1 concentration was >200 microg/g and chymotrypsin activity >6U/g. One test was below threshold in 19 percent, both in 15 percent. In patients with type 1 diabetes, the three groups defined by results of elastase-1 concentration and chymotrypsin activity differed with regard to duration of diabetes and prevalence of glutamic acid decarboxylase antibodies, but not BMI or HbA(1c), or prevalence of retinopathy, neuropathy, nephropathy or vascular disease. In patients with type 2 diabetes, but not BMI or HbA(1c), or prevalence of retinopathy, neuropathy, nephropathy or vascular disease. In patients with type 2 diabetes, but not BMI or HbA(1c), or prevalence of retinopathy, neuropathy, nephropathy or vascular disease. In patients with type 2 diabetes, but not BMI or HbA(1c), or prevalence of retinopathy, neuropathy, nephropathy or vascular disease. In patients with type 2 diabetes, but not BMI or HbA(1c), or prevalence of retinopathy, neuropathy, nephropathy or vascular disease. In patients with type 2 diabetes, but not BMI or HbA(1c), or prevalence of retinopathy, nephropathy or vascular disease.

the three groups differed with regard to BMI, use of insulin and vascular disease, but not known duration. It was concluded that factors associated with pancreatic exocrine failure differ in patients with type 1 diabetes compared with patients with type 2 diabetes. In patients with type 2 diabetes, association of decreased pancreatic exocrine function with BMI and vascular disease suggests a role of pancreatic arteriopathy [121].

Antioxidants

Chronic pancreatitis (CP) is an inflammatory disease characterized by the progressive destruction of pancreatic tissue and resulting in pancreatic exocrine and endocrine insufficiency. Increased oxidative stress has been implicated as a potential mechanism in its etiology and pathology. A number of studies have demonstrated that CP patients have a compromised antioxidant status, which may be a contributing factor to the enhanced oxidative state associated with the disease. Nutrition is an essential consideration in the treatment of CP, especially since diet is a source of several antioxidants and cofactors required for the production of cellular antioxidant enzymes. Many CP patients have an inadequate intake of macro and micronutrients because of abdominal pain and discomfort, which often increase postprandially and discourage eating. Exocrine insufficiency leads to further complications by preventing adequate digestion and absorption of ingested food, thus causing even greater deficiencies and impairment of antioxidant status [122].

Pain

Opioid therapy for pain in chronic pancreatitis (CP) is associated with tolerance and possibly opioid-induced hyperalgesia. It was thus examined opioid use and pain rating in CP patients. Medical records of patients with established CP treated between 2008 and 2009 were retrospectively reviewed. Two hundred nineteen unique patients (53 % men; age, 50 \pm 1 years) were identified. At least moderate pain was initially present in 37 percent of the patients. Half (51 %) of the patients received opioids (average morphine equivalent, 78 \pm 12 mg/d). Pain severity correlated with age, history of alcohol abuse, affective spectrum disorders, presence of coexisting pain syndromes, opioid use, and days with concerns about physical or mental problems. In contrast, computed tomography-defined pancreatic abnormalities (calcification, pseudocysts, ductal stones, or dilation) did not correlate with pain rating. Regression analysis identified age, days with physical problems, and a coexisting pancreatitis etiology, especially alcohol use, and psychosocial factors are important determinants of pain severity in CP [123].

Surgery

The most important symptom in patients with chronic pancreatitis is pain. This is often difficult to treat. The current treatment consists of, successively, optimal medical treatment, endoscopic intervention and finally surgical intervention. Previous research has indicated that early surgical intervention leads to better pain management and preservation of pancreatic function. Recently, the randomised multicentre "Early surgery versus optimal current step up practice for chronic-pancreatitis" (ESCAPE) trial was started in order to evaluate whether early surgery provides better reduction of pain in comparison with present treatment. In addition, serious complications, mortality, cost-effectiveness, quality of life, pancreas insufficiency, alternative pain scores, hospital admissions and the number of interventions will be assessed [124].

Pain caused by CP can be alleviated through operative intervention with type of procedure depending on anatomical abnormalities. Outcome measures include functional (pain relief, quality of life, QoL), medical (endo- and exocrine function), and clinical (reoperation) results reported by patient. It was measured a comprehensive set of outcome measures after different surgical procedures for painful chronic pancreatitis (CP) at long-term follow-up. A cross-sectional cohort of 223 consecutive patients who underwent surgical drainage, head resection, or left-sided pancreas resection, depending on anatomical abnormalities, was analyzed. Participating patients were reassessed during a prospectively scheduled outpatient clinic visit. At follow-up, 44 patients had died; 146 of 179 living patients consented to participate in the study. After 63 months (range: 14-268), 68 percent reported no or little pain, 19 percent reported intermediate pain, and 12 percent reported severe pain. Preoperative daily opioid use (OR 3.04; 95 % confidence interval 1.09 to 8.49) and high numbers of preceding endoscopic procedures (OR 3.89; 95 % confidence interval 1.01 to 14.9) were associated with persistent severe pain. Compared with the general population, physical more than mental QoL remained impaired. At follow-up, endocrine insufficiency was present in 57 percent of patients and exocrine insufficiency was present in 77 percent. Independently, a head resection and a reoperation for any cause were moderately associated with new-onset diabetes. Compared with patients who underwent left-sided resection, the risk of developing exocrine insufficiency after surgery was higher after drainage or head resection. After 20 months (interquartile range: 10-51) after surgery, 26 (12 %) of 223 patients underwent 1 or more elective reoperations. Operative intervention for painful CP, tailored to anatomical abnormalities, results in excellent to fair long-term pain relief, but approximately 10 percent of patients do not respond. QoL scores remained slightly compromised. High preoperative pain levels, suggested through daily opioid use and high numbers of endoscopic procedures, are associated with less favorable outcome [125].

Pancreaticoduodenectomy

Due to improved surgical outcomes and increased detection of pancreatic lesions, the resection of nonmalignant and indeterminate lesions of the pancreas has increased. One study aimed to assess the outcomes over an extended period of time and the clinical consequences of pancreaticoduodenectomy (PD) performed for nonmalignant indications. Patients undergoing a PD between 2006 and 2010 were retrospectively identified and asked to complete a symptom survey. Charts were reviewed for hospital admissions, emergency room visits, complications, and procedures performed. A total of 132 patients were identified through database review with a median follow-up of 3 years. Forty-two patients (31 %) completed the phone survey. Pain and diarrhea were the most common symptoms reported, negatively impacting the patient's daily life in 5 percent and 7 percent of patients, respectively. Diabetes developed or worsened in 20 percent, with new insulin required in 12 percent. Complications were rare, with abdominal abscess (7.6%) occurring most commonly. Although some patients experienced symptoms that negatively impacted their daily life or had diabetic issues following surgery, the outcome of patients undergoing PD for nonmalignant indications was generally favorable [126].

Pancreaticoduodenectomy versus duodenum-preserving pancreatic head resection

The objective of one study was to assess the efficacy and safety of pancreaticoduodenectomy (PD) and duodenum-preserving pancreatic head resection (DPPHR) for the treatment of chronic pancreatitis (CP). The 123 patients with CP who underwent pancreatic head resection between 2004 and 2009 were retrospectively analyzed. The preoperative variables, operative data, postoperative complications, and follow-up information were examined. There were no significant differences in clinical and morphological characteristics, pain relief, and jaundice status between the PD and DPPHR groups. The duration of operation was shorter (252 vs 325 minutes), blood loss was less (464 vs 647 mL), and overall postoperative morbidity was lower (3 % vs 19 %) in DPPHR group. The duration of hospital stay was also significantly different (10 vs 14 days). Most functional and symptom scales revealed a better quality of life in DPPHR group. The proportion of patients with exocrine and endocrine insufficiency was higher in PD group as compared with DPPHR group. It was concluded that both procedures are equally effective in pain relief, but DPPHR is superior to PD in operative data, postoperative morbidity, improving quality of life, and preservation of exocrine and endocrine function [127].

Total pancreatectomy and islet autotransplantation

Total pancreatectomy (TP) with intraportal islet autotransplantation (IAT) can relieve pain and preserve β-cell mass in patients with chronic pancreatitis (CP) when other therapies fail. It was reported on a >30-year single-center series. Four hundred and nine patients (including 53 children, 5 to 18 years) with CP underwent TP-IAT from 1977 to 2011 (etiology: idiopathic 41 %; Sphincter of Oddi dysfunction/biliary 9 %; genetic 14 %; pancreas divisum 17 %; alcohol 7 %; and other 12 %; mean age was 35 years, 74 % were female; 21 % has earlier operations, including 9 % Puestow procedure, 6 % Whipple, 7 % distal pancreatectomy, and 2 % other). Islet function was classified as insulin independent for those on no insulin; partial, if known C-peptide positive or euglycemic on once-daily insulin; and insulin dependent if on standard basal-bolus diabetic regimen. A 36-item Short Form (SF-36) survey for quality of life was completed by patients before and in serial follow-up since 2007, with an integrated survey that was added in 2008. Actuarial patient survival post TP-IAT was 96 percent in adults and 98 percent in children (1 year) and 89 percent and 98 percent (5 years). Complications requiring relaparotomy occurred in 16 percent and bleeding (10 %) was the most common complication. IAT function was achieved in 90 percent (C-peptide >0.6 ng/mL). At 3 years, 30 percent were insulin independent (25 % in adults, 55 % in children) and 33 percent had partial function. Mean hemoglobin A1c was <7.0 percent in 82 percent. Earlier pancreas surgery lowered islet yield (2.712 vs 4.077/kg). Islet yield (<2.500/kg, 36 %; 2,501 to 5,000/kg, 39 %; >5,000/kg, 24 %) correlated with degree of function with insulinindependent rates at 3 years of 12, 22, and 72 percent, and rates of partial function 33, 62, and 24 percent. All patients had pain before TP-IAT and nearly all were on daily narcotics. After TP-IAT, 85 percent had pain improvement. By 2 years, 59 percent had ceased narcotics. All children were on narcotics before, 39 percent at follow-up; pain improved in 94 percent; and 67 percent became pain-free. In the SF-36 survey, there was significant improvement from baseline in all dimensions, including the Physical and Mental Component Summaries, whether on narcotics or not. It was concluded that TP can ameliorate pain and improve quality of life in otherwise refractory CP patients, even if narcotic withdrawal is delayed or incomplete because of earlier long-term use. IAT preserves meaningful islet function in most patients and substantial islet function in more than two thirds of patients, with insulin independence occurring in one guarter of adults and half the children [128].

The most evident symptom of CP is recurrent or chronic abdominal pain. This pain can be so debilitating that children are unable to attend school or perform any normal activity due to frequent hospitalizations. Growing up under such conditions may lead to depression, and the combination of the pain and depression frequently results in a dependence on narcotic analgesics. Once medical treatments are no longer efficacious, the only possible solution is surgical treatment. Surgical options to treat CP depend on etiology and the morphologic consequences of the disease. Some patients are candidates for endoscopic pancreatic ductal drainage, and others for resection treating a focal disease. Once specific medical treatments and endoscopic interventions are no longer efficacious, total pancreatectomy is the alternative of choice for helping the patient to achieve pain control. While daily administrations of digestive enzymes cannot be avoided, insulin-dependent diabetes can be prevented by transplanting the isolated pancreatic islets back to the patient. However, otal pancreatectomy is reserved for diffuse changes, where no other surgical options are

reasonable. Besides the life-long need for substituting the exocrine function of the pancreas, the endocrine function is also lost. To reduce the severe consequences of the complete removal of the pancreas and to save part of the endocrine function at least for a time, the isolated islets of Langerhans can be returned to the patient by injecting them into the portal vein, so that they will eventually make their "home" in the sinusoids of the liver. Isolation of islets from the pancreas of young individuals is technically challenging even when dealing with healthy donor organs. The concern of producing an adequate yield of islets from pancreata affected by CP has been one of the limiting factors in undertaking this procedure. The greater the number of islets infused, the greater the chance to prevent or at least control the effects of surgical diabetes. It was presented a technical approach for the isolation and preservation of the islets proven to be efficient to obtain high numbers of islets, favoring the successful treatment of young patients [129].

Chronic pancreatitis represents a very debilitating and serious disorder, particularly in juveniles. The decision to perform a total pancreatectomy is a weighty one considering both short-term and long-term morbidity. Although it is up to the gastroenterologist's expertise to treat this disease and to decide when all the available routes of intervention have been exhausted, once surgical removal of the pancreas becomes an option, it is important to consider islet cell autotransplantation to reduce or eliminate a major source of morbidity, diabetes. The surgical intervention is unchanged whether autoislets are reinfused, regardless of the potential residual endocrine function. If the islets are not given back to the patient, they will be discarded. Rather than not using the islets, even minimal endocrine function returned to the patient, ethically and clinically justifies the procedure of islet isolation and autotransplantation. It was believed that any additional risk, which is generally minimal to the patient would be more than outweighed by the benefit, even considering limitations such as the quality and quantity of the available islets, deteriorated as they are after the prolonged inflammation of the organ, and the less than ideal location of the infusion into the liver. Even if the islets available for transplantation are limited in mass, it is proven that a limited quantity of physiologically generated insulin can be of great advantage for the patient. Administrations of recombinant insulin could be completely avoided or the quantity reduced. Although the variables that clinically influence the efficiency of each transplant are high in numbers so that a direct relationship between IEQ/kg and C-peptide production is difficult to demonstrate, we can agree that the previously determined threshold of 2500-3000 IEQ/kg is associated with most successful clinical results. From the islet allotransplantation setting, we also learned that even minimal quantities of insulin and C-peptide can reduce, respectively, hypoglycemia unawareness and its frequently tragic consequences, as well as the blood vessel atherosclerotic deterioration, principal cause of all typical diabetes complications [129].

Some CP patients, because of family history or genetic mutations, have a higher risk for developing pancreatic cancer. A pancreatectomy will, of course, remove this risk. However, the question remains if it is safe to isolate and return the islets to these patients. Research into this question is still relatively new; however, it appears that in these cases an autotransplant of islets into the liver does not increase the risk of the patient developing cancer. The death of the majority of the acinar cells during the isolation procedure and the reduced quantity of ductal material remaining after isolation may explain these positive results. An autotransplanted pancreatic islet or just beta-cells, allows in the absence of a need for immunosuppression not only for a better engraftment of the islets, but also for a potentially longer graft survival time than is observed for the islets used in allotransplantation. The improved survival is due in part to the absence of rejection, and in part to the fact that the most used immunesuppressive regimens include drugs that are toxic for the insulinproducing beta cells. The frequently less than lifelong survival of the graft might not be due entirely to the stress that the isolation protocol itself imposes on the islets, but also to the less than ideal site of the infusion. The sinusoids of the liver, while optimal to guarantee blood exposure to the islets and a proper geographical location – being a part of the portal system in which insulin is physiologically secreted – might not be the most suited site for properly

lodging them. It is demonstrated that the islets transplanted into the liver accumulate amyloid deposits that, not only damage the liver's structure, but also tends to physically isolate the transplanted tissue, reducing its ability to obtain sufficient oxygen and nutrients. While looking for more suitable sites, the present possibility of providing some diabetes-free years or at least years of reduced insulin needs, still supports the procedure of islet autotransplantation. If, in many cases, the characteristics of the pancreas are such that they do not allow for the harvest of a sufficiently large mass of islets to completely satisfy the recipient's insulin needs, a very sizeable improvement has been obtained adapting our isolation procedure to better digest the pancreas damaged by CP. It has been found that by optimizing the perfusion of collagenases through the entire pancreas, by a technique in which we clamp any leaks, allows for a more complete digestion. In addition, a longer period of this stationary digestion is particularly beneficial to younger patients in producing a larger yield of islets. Another hallmark of our process is the flexibility in the management of the digestion, tailoring the amount of stationary and mechanical digestion based on direct monitoring of the islets released under the microscope rather than rigidly following a fixed standard of timing. The number of successful islet autotransplants in young patients supports our positive conclusions and leads to continue to search for alternative ways to better digest the organ, better protect the islets during the isolation, and find a more suitable site to transplant the isolated islets [129].

Total pancreatectomy and islet autotransplantation (TP/IAT) is a treatment option in a subset of patients with chronic pancreatitis. A systematic review of the literature was performed to evaluate the outcome of this procedure, with an attempt to ascertain when it is indicated. MEDLINE (1950 to present), Embase (1980 to present) and the Cochrane Library were searched to identify studies of outcomes in patients undergoing TP/IAT. Cohort studies that reported the outcomes following the procedure were included. The MOOSE guidelines were used as a basis for this review. Five studies met the inclusion criteria. The techniques reported for pancreatectomy and islet cell isolation varied between studies. TP/IAT was successful in reducing pain in patients with chronic pancreatitis. Comparing morphine requirements before and after the procedure, two studies recorded significant reductions. Concurrent IAT reduced the insulin requirement after TP; the rate of insulin independence ranged from 46 percent of patients at 5 years' mean follow-up to 10 percent at 8 years. The impact on quality of life was poorly reported. The studies reviewed did not provide evidence for optimal timing of TP/IAT in relation to the evolution of chronic pancreatitis. Thus, the systematic review showed that TP/IAT had favourable outcomes with regard to pain reduction. Concurrent IAT enabled a significant proportion of patients to remain independent of insulin supplementation [130].

Robot-assisted pancreatoduodenectomy

For patients with chronic pancreatitis presenting with medically intractable abdominal pain, surgical intervention may be the only treatment option. However, extensive pancreatic resections are typically performed open and are associated with a substantial amount of postoperative pain, wound complications and long recovery time. Minimally invasive surgery offers an avenue to improve results; however, current limitations of laparoscopic surgery render its application in the setting of chronic pancreatitis technically demanding. Additionally, pancreatic resections are associated with a high incidence of diabetes. Transplantation of islets isolated from the resected pancreas portion offers a way to prevent post-surgical diabetes; however, preservation of the vascular supply during pancreatic resection, which determines islet cell viability, is technically difficult using current laparoscopic approaches. With recent advances in the surgical field, robotic surgery now provides a means to overcome these obstacles to achieve the end goals of pain relief and preserved endocrine function. It was presented the first report of a novel, minimally invasive robotic approach for resection of the pancreatic head that preserves vascular supply and enables the isolation of a high yield of viable islets for transplantation. Minimal warm

ischemia time (less than three minutes) and excellent islet recovery (134,727 islet equivalent) was obtained. The patient is currently pain-free with normal glycemic control. Robot-assisted pylorus-preserving pancreatoduodenectomy and autologous islet transplantation can be safely performed and has the potential to minimize operative traumas as well as to partially preserve endocrine function. Results from this case report suggest that this dual procedure should be considered as a treatment option for patients with chronic pancreatitis at earlier stages of the disease, before irreversible islet loss occurs [131].

Surgery versus endoscopic pain treatment

The early stages of chronic pancreatitis are characterized by frequent painful episodes, which usually disappear over time. Currently, endoscopy is a bridge to surgery for patients who are in a critical condition and cannot immediately undergo surgery. Surgery in carefully selected patients remains the best approach to treating chronic pancreatitis. The clinical course of chronic pancreatitis is characterized by frequent painful episodes in its early stages. The pain tends to disappear during the course of the disease (the so-called burn-out phenomenon) or within 10 years of disease onset, as the destruction of the gland is clinically evident with the appearance of steatorrhea and diabetes. Pain is the only clinical symptom capable of drastically impairing a patient's quality of life; therefore, controlling pain is the main therapeutic aim in patients with chronic pancreatitis. Efforts should be increased to identify efficacious therapies capable of controlling this symptom. Pain from chronic pancreatitis has numerous causes, including both pancreatic and extrapancreatic factors. The extrapancreatic causes are mainly related to duodenal stenosis, which can be associated with stenosis of the main biliary duct. Pain caused by pancreatic factors seems to have a neuropathic origin. However, the pain can be the result of various different mechanisms. Thus, an optimal cure requires a treatment capable of controlling the various mechanisms of pain. Until now, surgical and endoscopic therapies have been considered as alternative, rather than complementary, approaches to treating pain in patients with chronic pancreatitis, and the controversy surrounding their efficacy is ongoing. Several studies have attempted to show the superiority of the endoscopic approach over the surgical option and vice versa. A study published in 2003 included 72 patients with chronic pancreatitis who were randomly assigned to undergo surgery (resection or drainage) or endotherapy (sphincterotomy and stenting and/or stone removal). Although the initial success rates were similar for both groups, at the 5-year follow-up, the complete absence of pain was more frequent after surgery than after endoscopy (37 % vs 14 %), with the rate of partial relief being similar for the two procedures (49 % vs 51 %). The authors concluded that surgery was superior to endotherapy for long-term pain reduction in patients with painful obstructive chronic pancreatitis. They also suggested that an improved selection of patients for endotherapy could be helpful in maximizing results. These findings were received with skepticism by endoscopists for various reasons, the main one being that the treatment was tailored to the patient. Several other papers utilizing sphincterotomy, dilation of strictures and removal of stones have claimed that endoscopic therapy is useful in patients with chronic pancreatitis. A comparative study has assessed the long-term results of endoscopic versus surgical treatment of patients with chronic pancreatitis. The authors randomly assigned 39 symptomatic patients to receive endoscopic transampullary drainage with or without lithotripsy or a pancreaticojejunostomy. Rates of complications, length of hospital stay and changes in pancreatic function were similar in the two treatment groups, but patients receiving endoscopic treatment required more procedures than the patients in the surgical group. Once again, surgical drainage of the pancreatic duct was more effective than endoscopic treatment in patients with obstruction of the pancreatic duct attributable to chronic pancreatitis (complete or partial pain relief in 75 % and 32 % of patients, respectively). The same group of authors also evaluated the long-term outcome of these patients after 5 years and found that symptomatic patients with advanced chronic

pancreatitis who underwent surgery as the initial treatment for pancreatic duct obstruction had more relief from pain, with fewer procedures, than patients who were treated endoscopically. Notably, 47 percent of the patients in the endoscopy group eventually underwent surgery. More recently, Clarke et al have provided further information on this topic. The authors evaluated the utilization and long-term effectiveness of endoscopic therapy in a retrospective series of 146 patients with chronic pancreatitis, of whom 49 percent received endoscopic therapy. The success of the endoscopic therapy and that of surgery was defined as the cessation of narcotic therapy and the resolution of episodes of acute pancreatitis. Disease progression was followed for a mean of 8 years. On the basis of imaging, patients who underwent endoscopic therapy had a more complex pancreatic morphology and more symptoms (such as pain and recurrent pancreatitis) than those who received medical therapy; endoscopic therapy had a high rate of technical success (85%). However, it should be noted that the patients who responded to endoscopic therapy were older, had a shorter disease duration before endoscopic therapy, had less constant pain and required fewer daily narcotics than patients who did not respond to endoscopic therapy; thus, as usually happens in retrospective studies, a bias of selection is present. Of the 36 symptomatic patients who received medical therapy and were followed for a mean of 6 years, 31 percent improved and 53 percent had no change in symptoms (21 % of these underwent surgery). Thus, these results seem to emphasize the fact that intensive conservative treatment should also be utilized before surgically or endoscopically treating patients with chronic pancreatitis. At present, surgery remains the best approach for patients with chronic pancreatitis, also removing the local causes of nervous pain; however, we should also remember that, for surgical treatment of the pain in these patients, careful selection of patients is the main factor in achieving improved results. The endoscopic approach should be considered as a bridge to surgical treatment for those patients who are candidates for surgery but are initially unfit for the procedure as a result of their critical clinical condition [132].

Bilateral thoracoscopic splanchnicectomy

Bilateral thoracoscopic splanchnicectomy (BTS) is a well-known technique to alleviate intractable pain in patients with chronic pancreatitis. BTS not only disrupts afferent fibers from the pancreas that mediate pain but also postganglionic sympathetic fibers, which originate in segments T5-T12 and which innervate the vasculature of the liver, pancreas, and the adrenal gland. The purpose of this study was to assess whether and how BTS affects sympathetic noradrenergic and adrenomedullary function in patients with chronic pancreatitis. Sixteen patients with chronic pancreatitis for at least 1 year underwent autonomic function testing before and 6 weeks after BTS for intractable pain. Testing was performed during supine rest and during sympathetic stimulation when standing. Supine and standing systolic and diastolic blood pressure were significantly lower post-BTS compared with pre-BTS. One patient showed orthostatic hypotension after BTS. Baseline plasma norepinephrine levels and plasma norepinephrine responses to sympathetic activation during standing were not reduced by BTS. In contrast, supine plasma epinephrine levels and responses during standing were significantly reduced. Parasympathetic activity was unaffected by BTS as shown by unaltered Valsalva ratio, I-E difference, and deltaHRmax. It was concluded that BTS for pain relief in patients with chronic pancreatitis reduced adrenomedullary function, due to disruption of the efferent sympathetic fibers to the adrenal gland. BTS did not affect noradrenergic sympathetic activity, although blood pressure was lower after the sympathectomy [133].

Pancreatopleural fistulae

Pancreaticopleural fistula has been recognized as a clinical entity since case reports were published in late 1960s. Since that time, pancreaticopleural fistulae and pancreatic ascites have been termed as internal pancreatic fistulae which share common pathogenesis which includes the disruption of main pancreatic duct, resulting in leakage of pancreatic fluid. This rare entity may be seen in patients with acute and chronic pancreatitis or may follow traumatic and surgical disruption of the pancreatic duct. It is characterized by massive pleural fluid and has a tendency to recur following treatment. While conservative management with pancreatic duct stenting and inhibition of pancreatic secretion with octreotide may achieve closure of fistula in 31 to 45 percent of cases, surgery leads to healing in 80 to 90 percent of cases but carries a mortality up to 10 percent. Pleural effusion due to pancreaticopleural fistula is extremely unusual accounting for less than 1 percent of cases. It is seen in 3 to 7 percent of patients with pancreatitis, and a combined frequency of internal pancreatic fistula (pancreatic ascites and pancreaticopleural fistulae) is seen in between 0.4 and 7 percent of chronic pancreatitis patients and in 6 and 14 percent of patients with pseudocyst. Pancreaticopleural fistulae are however more unusual than pancreatic ascites. It usually presents as large recurrent pleural effusion in either pleural space, but left-sided effusion is more common and is reported to account for 76 percent of cases. The development of pancreaticopleural fistula is usually a consequence of leak from an incompletely formed or ruptured pseudocyst or in a minority of cases due to direct pancreatic duct leak. The fistulous tract passes either through the aortic or oesophageal diaphragmatic orifice or directly transdiaphragmatically. Similar pathophysiology and aetiology apply to pancreatic ascites and pancreatic pleural effusion. If the pancreatic duct disruption occurs anteriorly and is not walled off, a pancreaticoperitoneal fistula will develop that will manifest as ascites. If the disruption develops posteriorly, pancreatic secretion will flow into retroperitoneum and may dissect through aortic or oesophageal hiatus into mediastinum and form a pleural fistula or present as mediastinal pseudocyst which in turn ruptures into the pleural cavity and forms a pleural fistula [134].

Middle-aged men between 40 and 50 years who have history of chronic alcoholism and develop pancreatitis, form the common group of patients who develop pancreaticopleural fistula. About half of the patients do not have history of pancreatitis. Trauma is less common cause and is seen in 0.5 percent of the cases. Pancreatic pseudocyst may be noted in 69 to 77 percent of the patient, who develop pancreaticopleural fistula. The clinical manifestations are often misleading as symptoms are usually associated with significant pleural effusion and consist of dyspnea, cough, chest pain fever and septicaemia. Pulmonary symptoms are more common than abdominal symptoms and are usually the presenting symptom with dyspnea being the most common. Rarely do patients complain of abdominal pain typical of acute pancreatitis. The average duration of symptoms is 6 weeks. Pleural effusion are predominately left sided; however, right-sided and bilateral effusion occurs in 19 and 14 percent of patient's, respectively. Pleural effusion of this nature tends to be large and recurrent despite repeated thoracocentesis. Many patients go through extensive pulmonary evaluation before pancreas is identified as the site of primary pathology. The pleural effusion is associated with ascites in 20 percent and pericarditis in 4 percent. The major complication in these patients is superinfection which contributes to significant morbidity and mortality. Frequently the diagnosis is delayed. The time to diagnosis is reported to range from 12 to 49 days. Delay in diagnosis is a critical issue. It needs a high index of clinical suspicion in those with a history of acute pancreatitis and alcohol abuse presenting with a pleural effusion which reforms relatively rapidly after aspiration and for which there is no obvious other cause. Pleural effusion associated with pancreaticopleural fistula should be distinguished from the small reactive, self-limiting left-sided effusion that commonly occurs in 3 to 17 percent of patients with acute pancreatitis. A pancreaticopleural fistula may be suspected on the basis of the clinical picture and analysis of pleural fluid following thoracocentesis which reveals an extremely elevated pleural fluid amylase level (normal <150 IU/L), lipase, and high albumin

content (>3 g/dL). The serum amylase on the other hand is usually mildly elevated but not invariably and is thought to be partly secondary to reabsorption of amylase from pleural surfaces. The differential diagnosis for amylase-rich pleural effusion includes acute pancreatitis, cancer of lung, rectum, breast, female reproductive system, metastatic carcinoma, pneumonia, oesophageal perforation, lymphoma, leukaemia, liver cirrhosis, hydronephrosis, and pulmonary tuberculosis. A simple chest radiography is the first line of investigation, but this provides only limited information of the fluid collection in pleural cavity. A CT scan of the chest and abdomen is valuable in the diagnosis. Currently CT is the gold standard for investigating pleural effusion. It is very useful in determining the site and size of effusion, but overall ability to provide accurate delineation of the fistula is disputable. CT abdomen in addition will reveal changes of pancreatitis and identify other associated abnormalities such as pancreatic pseudocysts. CT scan may demonstrate the fistulous tract especially if obtained immediately after an ERCP. Magnetic resonance cholangiopancreaticography is reported to be particularly useful in demonstrating the pancreatic pathology and the fistula. It is a noninvasive alternative to ERCP, visualizes the duct beyond the strictures, depicts parenchymal atrophy, ductal anatomy and small intrapancreatic extrapancreatic pseudocyst, peripancreatic and collection, or pancreaticopleural fistula, and is useful where ERCP fails to give adequate information. The diagnosis may be confirmed with ERCP although it may not always be possible to demonstrate the fistulous tract. ERCP may not demonstrate the fistula in patients in whom the site of ductal disruption exists in more distal side than the site where a ductal obstruction exists. In these cases, CT or MRCP may be helpful. ERCP leads to diagnosis in 80 percent of cases and demonstrates the fistulous tract in 59 to 74 percent of the cases [134].

Due to high failure rate in the past of simple conservative management including drainage of chest and keeping the patient nil per oral, the patient would invariably require surgical intervention. Following the encouraging results with octreotide administration and stent placement, success rate of conservative management has significantly improved. The available treatment modalities now include

- conservative/medical management (octreotide and thoracentesis)
- ERCP plus/minus endoscopic pancreatic stent placement
- surgery

The aim of the medical treatment is to reduce stimulation to pancreatic exocrine secretions. Medical treatment constitutes thoracocentesis and/or tube thoracostomy, both of which encourage apposition of serosal surfaces and symptom relief along with the administration of somatostatin analogues. The duration of this treatment by itself varies, but in the past when endoscopic stenting was not available, conservative management did not exceed 2 to 4 weeks. Within this time if there was failure to respond to conservative management, which includes failure of pleural effusion and or superinfection to clear, then surgical intervention would be the optimal treatment. Presently, due to the success achieved with octreotide administration and placement of stent in the duct, longer period of conservative management is employed; this includes octreotide being continued from 3 to 6 months and chest being drained from 6 to 24 days. Octreotide is given as an initial dose of 50 microg, administered subcutaneously three times a day, and the dose is titrated based upon the fistula output, the maximal dose employed being 250 microg three times daily. It is reported that octreotide significantly reduces fistula output and decreases the time to fistula closure. Measures like the prohibition of oral intake, nasogastric tube insertion and total parenteral nutrition used in the past are no longer necessary. Complications related to nonoperative therapy including malnutrition, central venous catheter infections, deep vein thrombosis, and sepsis associated with intestinal mucosal atrophy from prolonged fasting have been significantly reduced following the use of octreotide and pancreatic stent placement. Moreover, substantial overall morbidity and cost accrued due to prolonged hospitalization are reduced [134]

ERCP and stent placement have revolutionized the concept of nonsurgical management in these patients. The potential benefits of ERCP include papillary sphincterotomy in cases of sphincter of Oddi dysfunction, dilatation of stenosis of the main pancreatic duct, and extraction of stones from the main pancreatic duct with or without extracorporeal lithotripsy, all of which could contribute to persistence of the fistula. Mere endoscopic papillotomy may precede the insertion of the stent as a lesser option in those cases where stenting fails. When stents are placed into the main pancreatic duct, patient's pain caused by ductal pressure may be relieved; moreover, pseudocysts that communicate with the main pancreatic duct may be drained. ERCP also facilitates drainage of fistula by the insertion of nasopancreatic drains for 1 week, followed by placement of an endoprosthesis in the pancreatic duct. The distinct advantage of naso pancreatic drain in contrast to stent placement is that it allows pancreaticograms to be obtained repeatedly without further invasive procedures. It also allows application of low intermittent suction, which may potentially facilitate closure of a leak or fistula. However, the major drawbacks include the necessity for continued hospitalisation and patient discomfort due to the presence of the tube in the nose. ERCP in general is an invasive procedure, and the availability of expertise in endoscopic placement of stent is a bare necessity. The main objective of stent placement other than decompressing the duct is to bridge the site of duct disruption if possible. Most fistulae appear to arise from head or body of the pancreas and are thus amenable to bridging with a pancreatic stent. However bridging may not be feasible in patients in whom the fistula arises from the tail of the pancreas and the stent may have to be placed close to the duct disruption. Bridging pancreatic stents helps to close the fistula rapidly by decreasing the ductal pressure and abolition of pancreatic pressure gradient, achieved by bypassing the sphincter of Oddi and stricture and by mechanically blocking the fistula lumen. The stents used for this purpose are either 5 Fr or 7 Fr size. Fistulae from a pseudocyst which is no longer in direct communication with pancreatic ductal system may heal spontaneously. The principal aim of the treatment with stent is to achieve drainage of ducts with fistulae in short term and drainage of the stenosed pancreatic duct in long term (2–12 months). The optimum duration of drainage for fistulae is unknown at present. This can vary from 4 to 12 weeks... One approach would be to assess the persistence of fistula by repeating ERCP at 6 weekly intervals and documenting the passage of dve into the chest. The concern, however, of longterm use of stent is that it itself causes ductal changes that do not always regress after its removal. As the data on the long-term consequence of pancreatic duct stent placement is lacking, a definite opinion is difficult to draw. Significant proportion of these patients, however, may still require surgery particularly for persistent, recurrent fluid collections secondary to stenosis or disruption of the main pancreatic duct. The issue of how long to continue with endoscopic treatment is largely unresolved [134].

Surgical treatment is safe and effective and is appropriate either when medical management fails or where underlying condition requires surgical intervention. The main indications for surgery are failure of conservative and endoscopic treatment, obstruction of pancreatic duct that cannot be managed endoscopically and a symptomatic fit patient. Surgical treatment includes either some form of a pancreatic resection or enteropancreatic anastomosis to the site of pancreatic duct leakage or to the pseudocyst. If there is an obstruction of the main pancreatic duct proximal to the fistula, surgical treatment is necessary to decompress the obstructed duct with or without excision of the involved portion of the obstructed pancreas. Cystogastrostomy, cystojejunostomy and distal and middle pancreatectomy are appropriate options in the setting of symptomatic pancreatic pseudocysts or pancreatic duct obstruction [134].

Pancreas divisum

The purpose of this study was to retrospectively assess the diagnostic performance of multidetector row computed tomography (MDCT) in an evaluation of pancreas divisum using endoscopic retrograde pancreatography (ERP) as the reference standard. It was analyzed 41 consecutive patients (14 cases of pancreas divisum and 27 cases of standard anatomy) who had undergone both MDCT and ERP for the evaluation of clinically diagnosed acute pancreatitis between 2004 and 2007. The CT reconstruction thickness and interval were both 3 mm. Two radiologists independently reviewed CT data, and the diagnostic confidence in determining the pancreatic ductal anatomy was scored using a five-point scale. CT detectability was correlated with the severity of pancreatitis and the degree of pancreatic necrosis based on the Balthazar index. With consensus, 16 of 41 cases (39 %) were evaluated as indeterminate. Ductal anatomy was correctly diagnosed in 23 of 41 cases (56 %). Eight of 14 cases (57 %) were correctly diagnosed as pancreas divisum. Standard anatomy was identified in 15 of 27 cases (56 %). The inter-observer agreement was substantial. Grade B or more pancreatitis and the presence of pancreatic necrosis significantly influenced the evaluation of ductal anatomy. Pancreas divisum was correctly diagnosed in the case of grade A acute pancreatitis. The CT detectability of pancreas divisum in patients with grade B or more pancreatitis is still relatively low even in the MDCT era [135].

The role of pancreas divisum (PD) as a cause of acute recurrent or chronic pancreatitis (AR/CP) is still a matter of debate. The aims of one study were to evaluate the frequency of PD diagnosed using magnetic resonance cholangiopancreatography (MRCP) in patients with AR/CP of unknown origin (n=40) after careful exclusion of all known causes and to test the hypothesis of an interaction between anatomical (PD) and functional genetic anomalies (SPINK1, PRSS1, or CFTR gene mutations or polymorphisms, n=19, 25, and 30, respectively) that could result in AR/CP. Patients with alcohol-induced pancreatitis (n=29) and subjects who had MRCP for a nonpancreatic disease (n=45) served as controls. PD frequency was 7 percent in subjects without pancreatic disease, 7 percent in patients with alcohol-induced pancreatitis, and 5, 16, 16, and 47 percent in those with idiopathic, and PRSS1-, SPINK1-, and CFTR-associated pancreatitis, respectively. There was no significant difference between idiopathic pancreatitis and the two control groups. The frequency of PD was higher in patients with CFTR gene-associated pancreatitis as compared with those with idiopathic and alcoholic pancreatitis and with those with SPINK1 and PRSS1 geneassociated pancreatitis. The frequency of PD was not different in patients with idiopathic pancreatitis as compared with controls, demonstrating that PD by itself is not a cause of pancreatitis. PD frequency was higher in patients with genetic pancreatitis, especially in those with CFTR mutations or polymorphisms, suggesting a cumulative effect of these two cofactors [136].

It has been partially dispel arguments that pancreas divisum (PD) causes pancreatitis, but fascinatingly indicate that PD associates with CFTR gene mutations predisposing to pancreatitis. This association, however, does not definitely confer a pathophysiological role for PD in pancreatitis but may denote that PD co-mingles with CFTR mutations without influencing pancreatitis or CFTR mutations influence pancreatic duct embryogenesis. We advise "idiopathic pancreatitis" patients with PD to undergo genetic testing. In lieu of CFTR mutations undertake no endoscopic/surgical procedure; if CFTR mutations are found, then refer patients for genetic counseling and withhold endoscopic/surgical therapy unless randomized studies show benefit [137].

The role of pancreas divisum as a pancreatic ductal anomaly able to induce acute or chronic pancreatitis is still under debate; some authors consider the pancreas as a variant of the pancreatic ductal system able to induce acute or chronic pancreatitis as a result of relative outflow obstruction, whereas others consider this finding a simple morphological anomaly of

the pancreatic ductal system without any clinical consequence. Based on the results of a multicenter prospective study carried out in Italy which enrolled 1,173 patients with acute pancreatitis, it was found that only 2 patients had pancreas divisum diagnosed on the basis of endoscopic retrograde cholangiopancreatography (ERCP) findings. In Italian chronic pancreatitis patients, pancreatic ductal abnormalities were detected in 6 percent of the patients (49 out of 865 patients: complete pancreas divisum in 41 patients, incomplete in 6, and annular pancreas in the remaining 2). The two problems of pancreas divisum remain: what is the best imaging technique for diagnosing it and then to assess whether or not it is caused by acute or chronic pancreatitis? For many years ERCP has been considered the only technique able to diagnose pancreas divisum and recently it has been confirmed that ERCP is superior to multi-detector row computed tomography (MDCT) in assessing the presence of a ductal anomaly compatible with pancreas divisum. It was retrospectively assessed the diagnostic performance of MDCT in an evaluation of pancreas divisum using ERCP as the reference standard, and analyzed 41 consecutive patients (14 cases having pancreas divisum and 27 cases having standard anatomy) who had undergone both MDCT and ERCP for the evaluation of clinically diagnosed acute pancreatitis. Ductal anatomy was correctly diagnosed by MDCT in 23 of the 41 cases (56 %). Eight of the 14 cases (57 %) were correctly diagnosed by MDCT as pancreas divisum. Standard anatomy was identified in 15 of the 27 cases (56 %). The inter-observer agreement was substantial. According to the Balthazar criteria, pancreatitis of grade B or higher and the presence of pancreatic necrosis significantly influenced the evaluation of ductal anatomy, and pancreas divisum was correctly diagnosed in the case of Balthazar grade A acute pancreatitis. Regarding the possibility of pancreas divisum as an etiological factor of acute or chronic pancreatitis, French authors evaluated the frequency of pancreas divisum diagnosed using magnetic resonance cholangiopancreatography (MRCP) in patients with recurrent acute or chronic pancreatitis of unknown origin after exclusion of all known causes and they also tested the hypothesis of an interaction between anatomical and functional genetic anomalies (SPINK1, PRSS1, or CFTR gene mutations or polymorphisms). Patients with alcohol-induced pancreatitis and subjects who underwent MRCP for a non-pancreatic disease were used as controls. The frequency of pancreas divisum was 7 percent in subjects without pancreatic disease, 7 percent in patients with alcohol-induced pancreatitis, and 5, 16, 16, and 47 percent in those with idiopathic, and PRSS1-, SPINK1-, and CFTR-associated pancreatitis, respectively. The frequency of pancreas divisum was higher in patients with CFTR gene-associated pancreatitis as compared to those with idiopathic and alcoholic pancreatitis and with those with SPINK1 and PRSS1 gene-associated pancreatitis. These findings seem to demonstrate that pancreas divisum by itself is not a cause of pancreatitis and other factors are required, such as genetic factors, to induce acute or chronic pancreatic diseases. In conclusion, the best imaging techniques to diagnose pancreas divisum are ERCP or MRCP, and this pancreatic ductal anomaly does not cause acute or chronic pancreatitis [138].

MRCP

Patients with pancreas divisum may develop pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosing pancreas divisum. Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive test reported to be highly accurate in diagnosing pancreas divisum. To evaluate the diagnostic accuracy of MRCP in detecting pancreas divisum it was reviewed patients who underwent both ERCP and MRCP. Patients who had diagnostic endoscopic pancreatograms (ERP) after MRCP comprise the study population. Secretin was given in 113/146 patients (S-MRCP). The remaining 33/146 patients had MRCP without secretin. In 7/33 patients who underwent MRCP without secretin (21 %), the studies were non-diagnostic and, therefore, this group was not further analyzed and the study focused on the S-MRCP group only. ERP identified pancreas divisum in 19/113 (17 %) patients. S-MRCP identified 14/19 pancreas divisum and was false-positive in three cases (sensitivity 73 %, specificity 97 %, positive predictive value 82. %, negative predictive value 95 %). Of the eight patients with inaccurate S-MRCP, 5 (63

%) had changes of chronic pancreatitis by ERP. This differs from the frequency of chronic pancreatitis by ERP in 24/105 (23 %) patients with accurate MRCP findings. The ERCP findings of chronic pancreatitis were more frequent among incorrect S-MRCP interpretations than among correct interpretations (odds ratio 5.5, 95 % confidence interval 1.3 to 25.3). MRCP without secretin is non-diagnostic for pancreas divisum in a significant proportion of patients. S-MRCP had a satisfactory specificity for detecting pancreas divisum. However, the sensitivity of S-MRCP for the diagnosis of pancreas divisum was modest at 73 percent. This is low compared to previous smaller studies, which reported a sensitivity of MRCP of up to 100 percent [139].

AUTOIMMUNE PANCREATITIS

Overviews

Autoimmune pancreatitis (AIP) and IgG4-associated cholangitis (IAC) are the recently recognized pancreatobiliary manifestations of IgG4-associated systemic disease (ISD). Clinically, ISD of the pancreas and/or biliary tree may mimic pancreatic cancer, sclerosing cholangitis, or cholangiocarcinoma. Patients often present with abdominal pain, weight loss, jaundice, itch, and biochemical signs of pancreatitis and cholestasis. Tomography may reveal enlargement of the pancreas or may mimic malignant pancreatic lesions, and cholangiopancreatography may disclose irregularities of the pancreatic duct and stenoses of the distal and/or proximal common bile duct and intrahepatic bile ductules. Serum immunoglobulin G4 (IgG4) is elevated in most patients but, unlike tissue IgG4-loaded plasma cell infiltrates, is not diagnostic of the disease. The application of consensus diagnostic criteria for laboratory investigations, imaging, and histologic findings can identify patients who qualify for corticosteroid treatment. The excellent response to immunosuppressive therapy suggests an immune-mediated etiology of the disease, but the exact pathophysiological mechanisms are still under investigation. Relapse may occur after tapering down of corticosteroids, which supports the rationale of maintenance immunosuppression after remission has been induced [140].

Autoimmune Pancreatitis (AIP) is a recently recognized chronic fibro-inflammatory disease of the pancreas. Although rare, its recognition continues to increase worldwide. Patients often present with painless obstructive jaundice mimicking pancreatic cancer. Two subtypes of AIP are known-type 1 is a multi-organ disease associated with IgG4; type 2 appears to be a pancreas-specific disorder. Dramatic response to steroid treatment is characteristic of both forms. A non-invasive diagnosis of type 1 AIP may be possible using diagnostic criteria (in 70 % cases) while diagnosis of type 2 requires histology. These subtypes differ in natural history- type 1 often relapses while initial reports suggest that type 2 does not. Long term complications include endocrine and exocrine insufficiency and in case of type 1, disease relapses and complications from extra-pancreatic involvement. Neither form affects long term survival. The treatment and follow-up guidelines continue to evolve with the increasing experience in AIP [141].

Autoimmune pancreatitis (AIP) is a particular form of chronic pancreatitis recognized as clinical entity only in recent decades. Peculiar clinical, serological, histological and radiological features make it different from other types of pancreatitis. The diagnosis of AIP represents a challenge for the clinicians. Particularly in its focal form, it shows several features in common with pancreatic adenocarcinoma. Both of these conditions, in fact, are often associated with obstructive jaundice, cause increase of the volume of the pancreas and can share the radiologic appearance of a focal mass. The autoimmune pancreatitis instead of pancreatic cancer regresses promptly after treatment with oral corticosteroids. Because of the different management of the two diseases a correct differential diagnosis is imperative. From 5 to 21 percent of AIP cases are diagnosed in patients after pancreatic resection performed for suspected malignancy. Still it is not identified a specific serological marker of AIP which can allow a definitive diagnosis of the disease. Both the diagnosis of pancreatic cancer as AIP is paid on the basis of different clinical tests: the diagnosis of pancreatic cancer requires imaging studies, laboratory tests and biopsy of the pancreas, while the diagnosis of AIP requires confirmation of the diagnostic histological, serological and radiological criteria, the involvement of other organs and a positive response to treatment with corticosteroids [142].

A systemic disease

Immunoglobulin G4-related systemic disease (IgG4-RSD) is a recently defined emerging entity characterized by a diffuse or mass forming inflammatory reaction rich in IgG4-positive plasma cells associated with fibrosclerosis and obliterative phlebitis. IgG4-RSD usually affects middle aged and elderly patients, with a male predominance. It is associated with an elevated serum titer of IgG4, which acts as a marker for this recently characterized entity. The prototype is IgG4-related sclerosing pancreatitis or autoimmune pancreatitis (AIP). Other common sites of involvement are the hepatobiliary tract, salivary gland, orbit, and lymph node, however practically any organ can be involved, including upper aerodigestive tract. lung, aorta, mediastinum, retroperitoneum, soft tissue, skin, central nervous system, breast, kidney, and prostate. Fever or constitutional symptoms usually do not comprise part of the clinical picture. Laboratory findings detected include raised serum globulin, IgG and IgG4. An association with autoantibody detection (such as antinuclear antibodies and rheumatoid factor) is seen in some cases. Steroid therapy comprises the mainstay of treatment. Disease progression with involvement of multiple organ-sites may be encountered in a subset of cases and may follow a relapsing-remitting course. The principal histopathologic findings in several extranodal sites include lymphoplasmacytic infiltration, lymphoid follicle formation, sclerosis and obliterative phlebitis, along with atrophy and destruction of tissues. Immunohistochemical staining shows increased IgG4+ cells in the involved tissues (>50 per high-power field, with IgG4/IgG ratio >40 %). IgG4-RSD may potentially be rarely associated with the development of lymphoma and carcinoma. However, the nature and pathogenesis of IgG4-RSD are yet to be fully elucidated and provide immense scope for further studies [143].

Epidemiology

In Japan

To clarify the clinico-epidemiological features of autoimmune pancreatitis (AIP) in Japan, the nationwide survey was conducted patients with AIP who had visited the selected hospitals in 2007 were surveyed. Autoimmune pancreatitis was diagnosed according to the Japanese clinical diagnostic criteria 2006. The study consisted of 2-stage surveys: the number of patients with AIP was estimated by the first questionnaire and their clinical features were assessed by the second questionnaire. The estimated total number of AIP patients in 2007 was 2790 (95 % confidence interval 2540 to 3040), with an overall prevalence rate of 2.2 per 100,000 populations. The number of patients, who were newly diagnosed as AIP, was estimated to be 1120 (95 % confidence interval 1000 to 1240), with an annual incidence rate of 0.9 per 100,000 populations. Gender ratio (male to female) was 3.7, and the mean age was 63 ± 11 years. Among the 546 patients whose clinical information was obtained, 88 percent of the patients presented high serum immunoglobulin G4 levels (\geq 135 mg/dL), and 83 percent received steroid therapy. The data represent the current clinical features of AIP in Japan. From the results, most AIP patients in Japan can be categorized to type 1 AIP according to the recent classification of AIP [144].

Biopsy of non-pancreatic organs

The aim of one study was to evaluate the specificity of the infiltration of digestive tract mucosa by immunoglobulin (Ig) G4-positive plasma cells in patients with autoimmune pancreatitis (AIP), as compared with normal or inflammatory mucosa. Plasma cell infiltration, CD138 and IgG4 immunostaining of digestive biopsies were compared in 4 groups of patients: AIP type 1 (n=19); AIP type 2 (n=4) with inflammatory bowel disease (IBD); IBD without pancreatic disorders (n=20); and controls (n=26). With AIP type 1 versus controls, more plasma cells were present in the gastric mucosa of AIP without difference concerning

IgG4+ plasma cells at any biopsy site. With AIP type 1 versus IBD, colonic mucosa was more often abnormal, and more CD138 and IgG4 plasma cells were counted in the colon biopsies of IBD. With AIP type 2 versus IBD, no difference for plasma cell and IgG4 infiltration was found. It was concluded that IgG4-positive plasma cells are not more numerous in the digestive mucosa of AIP patients than in controls, but they are more abundant in the colon of IBD patients than in AIP patients [145].

Diagnostics

The purpose of one study was to determine whether the choice for performance of endoscopic retrograde pancreatography (ERP) could be tailored to findings on computed tomography (CT) in patients with suspected autoimmune pancreatitis (AIP). Eighty-four AIP patients and 73 pathology-proven pancreatic cancer patients from a prospectively maintained database were retrospectively included. Computed tomography and ERP images were reviewed in consensus by 2 blinded radiologists. The diagnostic performance of CT alone and combined use of CT and ERP (CT-ERP) were compared. The area under the receiver operating characteristic curve of CT-ERP was significantly greater than that of CT alone (0.97 vs 0.87). When patients with AIP were divided into 2 subgroups according to CT features (typical vs atypical), 24 (69 %) of 35 AIP patients with atypical CT findings were correctly diagnosed with AIP at CT-ERP and received benefits from additional ERP. Endoscopic retrograde pancreatography had little added benefit in patients with typical CT findings for AIP (n=49), because no alternative diagnoses were established after ERP. It was concluded that in patients with suspected AIP, the decision to perform ERP could be tailored to findings on CT [146].

PET/CT

IgG4-related systemic disease (IgG4-RSD) is an emerging clinical entity about which much remains to be elucidated, in terms of its aetiology, pathogenesis, diagnosis, treatment and outcome. Autoimmune pancreatitis (AIP) and Mikulicz disease (MD) are the two major, wellstudied constituents of IgG4-RSD. AIP and MD have common characteristics of forming tumour-mimicking lesions that consist of lymphoplasmacytic infiltrates and fibrosclerosis with numerous immunoglobulin G4 (IgG4)-positive plasma cells, as well as various multi-organ 2-[(18)F]-fluoro-2-deoxy-d-glucose manifestations of laG4-RSD. positron-emission tomography/computed tomography (FDG PET/CT) enables the acquisition of whole-body images and provides functional information about disease activity; as such it has a valuable role in staging extent of disease, guiding biopsy, and monitoring response to treatment. However, FDG PET/CT is likely to be only one component of the management strategy, and clinical, laboratory, imaging and histological findings are crucial in the overall diagnosis of the condition. At present FDG PET/CT does not have a well-established role in the assessment of patients with IgG4-RSD and future prospective studies are required to define the costeffectiveness and clinical impact in this patient group more accurately [147].

Immunoglobulins

Regulatory T-cells

Autoimmune pancreatitis (AIP) is a newly recognized pancreatic disorder. Recently, International Consensus Diagnostic Criteria for AIP (ICDC) was published. In this ICDC, AIP was classified into Type 1 and Type 2. Patients with Type 1 AIP have several immunologic and histologic abnormalities specific to the disease, including increased levels of serum IgG4 and storiform fibrosis with infiltration of lymphocytes and IgG4-positive plasmacytes in the

involved organs. Among the involved organs showing extrapancreatic lesions, the bile duct is the most common, exhibiting sclerosing cholangitis (IgG4-SC). However, the role of IgG4 is unclear. It has been reported that regulatory T cells (Tregs) are involved in both the development of various autoimmune diseases and the shift of B cells toward IgG4, producing plasmacytes. One study showed that Tregs were increased in the pancreas with Type 1 AIP and IgG4-SC compared with control. In the patients with Type 1 AIP and IgG4-SC, the numbers of infiltrated Tregs were significantly positively correlated with IgG4-positive plasma cells. In Type 1 AIP, inducible costimulatory molecule (ICOS)(+) and IL-10(+) Tregs significantly increased compared with control groups. Our data suggest that increased quantities of ICOS(+) Tregs may influence IgG4 production via IL-10 in Type 1 AIP [148].

Infiltration of many IgG4-positive plasma cells (G4-Ps) is seen in IgG4-related diseases and in several "non-IgG4-related diseases," such as pilonidal sinus (PS) as well. The involvement of CD4CD25 regulatory T cells (CD4CD25 Tregs) in IgG4-related diseases has been reported. To see whether CD4CD25 Tregs are involved in autoimmune pancreatitis (AIP)/non-IgG4-related diseases with many G4-Ps, we investigated the amount of G4-Ps and CD4CD25 Tregs histologically in AIP/PS. Four AIP and 10 PS were immunostained with IgG4/Foxp3, a specific marker for CD4CD25 Tregs. Double immunohistochemistry and dual fluorescent immunohistochemistry were conducted to see the amount of CD4CD25 Tregs. All AIP and 30 percent of PS showed abundant G4-Ps. G4-Ps infiltrated diffusely for all AIPs and in a patchy pattern for PS at the abscess/granulation foci. Foxp3 immunostaining/double immunohistochemistry showed moderate to abundant CD4CD25 Tregs in AIP and abscess of PS, but few to moderate in granulation of PS. Dual fluorescent immunohistochemistry also showed many CD4CD25 Tregs in AIP. It was concluded that many CD4CD25 Tregs were seen in AIP lesions, abscess of PS, but not in granulation of PS, suggesting that the amount of CD4CD25 Tregs sometimes do not synchronize with that of G4-Ps and might relate to the inflammatory activity of both AIP and PS [149].

Population IgG4

The diagnosis of autoimmune pancreatitis (AIP) and immunoglobulin subclass 4 (IgG4)associated cholangitis (IAC) is based on imaging studies, serology, histology and a response to steroid therapy. The major serological finding is an elevation of the serum IgG4 concentration. Previous studies have shown that its sensitivity is about 70 percent and its specificity exceeds 90 percent at a cut-off of 140 mg/dL in selected patient populations. The aim of one study was to assess the performance of serum IgG4 as a diagnostic parameter in an unselected liver and pancreas clinic population. IgG4 was prospectively determined in 1412 patients and clinical diagnoses were recorded from a review of patient charts. The prevalence of AIP or IAC in the entire cohort was 1.1 percent (n=15). The sensitivity of IgG4 for the diagnosis of AIP and IAC was 80 percent and the specificity was 86 percent at a cutoff value of \geq 135 mg/dl. The positive predictive value and the negative predictive value were 6 percent and 100 percent, respectively. The most common differential diagnosis in patients with elevated IgG4 was liver cirrhosis. It was concluded that IgG4 has a reasonable sensitivity and specificity in a liver and pancreas clinic population, where liver cirrhosis appears to be the most frequent differential diagnosis for elevated IgG4 concentrations [150].

IgG4 and extrapancreatic lesions

Type 1 autoimmune pancreatitis (AIP) is characterized by the increase of serum immunoglobulin (Ig)G4 and abundant IgG4 plasma cell infiltration in the pancreas and various extrapancreatic lesions (EPL), which are proposed as IgG4-related disease. It was assessed the correlation between serum IgG4 and the number of EPL, and the association between serum IgG4 and the distribution of EPL in type 1 AIP patients. Serum IgG4 was measured in 35 type 1 AIP patients and 71 non-AIP patients. The clinical characteristics and

distribution of eight EPL were determined in 35 type 1 AIP patients. Serum IgG4 in type 1 AIP was significantly higher than in non-AIP. A total of 33 patients had EPL among 35 patients with type 1 AIP (94 %). There was a significant correlation between serum IgG4 and the number of EPL. Further, to assess the association between serum IgG4 and the distribution of EPL, type 1 AIP patients were divided into two groups: as abdominal localized EPL and systemic EPL. Both serum IgG4 and total numbers of EPL in systemic EPL were remarkably higher than those in abdominal localized EPL. Serum IgG4 cut-off value was 346 mg/dL to distinguish between abdominal localized EPL and systemic EPL according to the receiver-operator characteristic curve data. The findings indicated that serum IgG4 was useful in both the diagnosis of type 1 AIP and the detection of systemic EPL. The finding may help the concept and diagnostic criteria of IgG4-related disease with type 1 AIP [151].

Addresins

Type 1 autoimmune pancreatitis (AIP) is histologically characterized by dense lymphoplasmacytic infiltration and marked storiform fibrosis, manifestations associated with pancreatic ducts. Such periductal lymphocyte recruitment is thought to be elicited by dysregulation of mechanisms governing physiological lymphocyte homing. One study was undertaken to determine whether vascular addressins including peripheral lymph node addressin and mucosal addressin cell adhesion molecule 1 (MAdCAM-1) play a role in type 1 AIP histogenesis. Tissue sections of type 1 AIP and tumor-associated non-AIP chronic pancreatitis, as well as normal pancreas, were subjected to immunohistochemical analysis using vascular addressin-related antibodies. The number of periductal mouse endothelial cell antigen 79-positive high endothelial venule (HEV)-like vessels was increased in type 1 AIP relative to that seen in non-AIP chronic pancreatitis, whereas the number of MAdCAM-1positive HEV-like vessels did not differ between the 2 conditions. Mouse endothelial cell antigen 79 antigens are expressed on duct-forming epithelial cells not only in pancreas but also in salivary glands, which often harbor extrapancreatic lesions in type 1 AIP. It was concluded that type 1 AIP can be characterized by periductal induction of MECA-79-positive HEV-like vessels. MECA-79-positive 6-sulfo sialyl Lewis X-related carbohydrate antigens expressed on duct-forming epithelial cells could be associated with type 1 AIP pathogenesis [152].

Insufficiencies

Glucos intolerance

Glucose intolerance is often observed in autoimmune pancreatitis (AIP), although its longterm prognosis after steroid treatment (ST) is still unclear. A total of 47 patients with AIP were enrolled. On the basis of the change in hemoglobin A1c (HbA1c) and the use of diabetic medication, prognosis was classified into 3 categories, namely, "improved," "aggravated," and "unchanged." The relation between the result of an initial glucagon tolerance test (deltaCPR) and the later use of insulin during maintenance ST was examined in 20 patients. The transitions of homeostasis model assessment β cell and insulin resistance (HOMA-beta and HOMA-R) were analyzed in 16 patients. Glucose tolerance was improved in 6 patients (13 %), aggravated in 9 patients (19 %), and unchanged in 32 patients (68 %). All patients with deltaCPR less than 0.6 ng/mL were obliged to use insulin even after longterm observation, whereas all patients with deltaCPR more than 1.0 ng/mL were free from insulin therapy. Moreover, HOMA-beta showed significant improvement after ST (44 % to 56 % in median), and HOMA-R showed significant aggravation (1.30 to 1.78). Glucose tolerance that is too severely damaged may not recover fully even after ST. Thus, ST should be performed to preserve insulin secretion at the early stage of AIP [153].

Exocrine insufficiency

Functional evaluation of the pancreas is hindered by invasiveness and/or methodological difficulties. Endoscopic ultrasonography (EUS) provides with highly accurate images of pancreatic ducts and parenchyma. The aim of the study was to analyze the probability of pancreatic exocrine insufficiency (PEI) according to EUS criteria in patients with a diagnosis of chronic pancreatitis. A total of 128 consecutive patients (mean age, 52 years; 104 men) with chronic pancreatitis were prospectively included. Pancreatic exocrine insufficiency was diagnosed by the carbon 13-mixed triglyceride breath test. Endoscopic ultrasonography was performed and EUS criteria of chronic pancreatitis evaluated by 2 different experienced endosonographers who were blinded to the results of the pancreatic function test. Forty-eight patients (38 %) had PEI. The percentage of patients with PEI increased linearly with the number of EUS criteria. The presence of intraductal calcifications, hyperechogenic foci with shadowing, and dilation of the main pancreatic duct were significantly and independently associated to PEI. The probability of PEI in the presence of calculi in the main pancreatic duct is 80 percent and increases to 83 percent if, in addition, the main duct is dilated. Thus, endoscopic ultrasonography findings allow predicting the probability of PEI in patients with chronic pancreatitis and thus the need for pancreatic enzyme replacement therapy [154]

Differentiation against pancreatic adenocarcinoma

Autoimmune pancreatitis (AIP) is a newly described entity of pancreatitis in which the pathogenesis appears to involve autoimmune mechanisms. Based on histological and immunohistochemical examinations of various organs of AIP patients, AIP appears to be a pancreatic lesion reflecting a systemic "IgG4-related sclerosing disease". Clinically, AIP patients and patients with pancreatic cancer share many features, such as preponderance of elderly males, frequent initial symptom of painless jaundice, development of new-onset diabetes mellitus, and elevated levels of serum tumor markers. It is of uppermost importance not to misdiagnose AIP as pancreatic cancer. Since there is currently no diagnostic serological marker for AIP, and approach to the pancreas for histological examination is generally difficult, AIP is diagnosed using a combination of clinical, serological, morphological, and histopathological features. Findings suggesting AIP rather than pancreatic cancer include: fluctuating obstructive jaundice; elevated serum IgG4 levels; diffuse enlargement of the pancreas; delayed enhancement of the enlarged pancreas and presence of a capsule-like rim on dynamic computed tomography; low apparent diffusion coefficient values on diffusion-weighted magnetic resonance image; irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography; less upstream dilatation of the main pancreatic duct on magnetic resonance cholangiopancreatography, presence of other organ involvement such as bilateral salivary gland swelling, retroperitoneal fibrosis and hilar or intrahepatic sclerosing cholangitis; negative work-up for malignancy including endoscopic ultrasound-guided fine needle aspiration; and steroid responsiveness. Since AIP responds dramatically to steroid therapy, accurate diagnosis of AIP can avoid unnecessary laparotomy or pancreatic resection [155].

It was reported on a case of autoimmune pancreatitis presenting as pancreatic head cancer, which is extremely rare in Iran. Currently, on the PubMed database, no such cases exist. A 70-year-old Iranian man presented with recurrent abdominal pain, jaundice and elevated bilirubin and alkaline phosphatase levels. An abdominal computed tomography scan revealed a heterogeneous presence in the pancreatic head as well as dilated intra- and extrahepatic bile ducts. A common bile duct stent had been inserted. The patient was subsequently diagnosed with pancreatic head cancer.Due to his continued recurrent abdominal pain, our patient returned to the hospital. His levels of bilirubin, alkaline phosphatase and tumor markers were all normal but his immunoglobulin G4 and antinuclear

antibodies were extremely high. A biopsy of the pancreatic head heterogeneity by endoscopic ultrasonography was performed.Pathologic samples showed fibrosis associated with lymphoplasmacytic infiltration and no evidence of malignancy. A diagnosis of autoimmune pancreatitis was confirmed, the bile duct stent removed, and an appropriate treatment plan was undertaken [156].

Pancreatic and biliary manifestations of AIP mimic pancreaticobiliary cancers. Misdiagnosis of AIP can result in major surgery for a steroid-responsive disease. A review of the literature to identify current modalities for the diagnosis of autoimmune pancreatitis (AIP) with the objective of establishing a strategy to distinguish it from pancreaticobiliary cancers was published. Diagnostic criteria for AIP are based on histology, imaging, serology, extrapancreatic organ involvement, and response to steroid therapy. The most commonly involved extrapancreatic sites are bile duct, kidney, and retroperitoneum. The Mayo Clinic diagnostic strategy utilizes core biopsy of the pancreas and the Japanese strategy depends on a characteristic pancreatogram. The rate of operative intervention was similar with both strategies and none of the patients with cancer received steroid therapy. Immunoglobulin G subtype 4 (IgG4)-associated cholangitis mimics cholangiocarcinoma and presence of more than 10 IgG4-positive plasma cells/high power field on endoscopic biopsy of the bile duct was diagnostic for AIP in 88 percent patients. Biliary complications and early relapse are common after surgical resection and immunomodulatory drugs can maintain long-term remission. It was concluded that criteria based on histology, imaging, endoscopy, serology, extrapancreatic organ involvement, and response to steroid therapy improve the diagnostic vield for AIP. Application of diagnostic and therapeutic protocols by a multidisciplinary team will optimize outcomes with a decline in the rate of operative intervention for AIP, a steroidresponsive disease with propensity for relapse [157].

Differential diagnosis

It is at present known and accepted that immunoglobulin G4 (IgG4)-associated cholangitis (IAC) is one of several diseases associated with autoimmune pancreatitis (AIP). However, IAC may occur in 20-90 percent of cases of AIP whereas a study of the Mayo Clinic recently revealed that 93 percent of patients with IAC suffer from AIP. A possible involvement of Helicobacter pylori in the initiation of the autoimmune process is speculated. Typical results concerning blood values are high IgG4 concentrations, which can be seen as a useful indicator to differentiate between other pancreatic or bile duct diseases. IgG4-related diseases such as AIP and IAC have typical histopathological features in common showing a diffuse infiltration with lymphocytes and IgG4-positive plasma cells. The acute syndrome appears with obstructive jaundice (30-100 %), diabetes mellitus (40-70 %), abdominal pain (35 %), and weight loss (30 %). Typical changes in pancreatic tissue are diffuse pancreatic swelling ("diffuse type") or a focal pancreatic mass ("focal type") with local lymphadenopathy and peri-pancreatic capsule-like rim. IAC is characterized by bile duct wall thickening and biliary strictures, which are, in contrast to primary sclerosing cholangitis, predominantly located in the lower bile ducts. Both AIP and IAC respond well to steroid therapy. Although there is no accepted consensus concerning the dose of steroid therapy, an initiation of prednisolone with 0.6 mg/kg/day followed by steroid dose tapering has been demonstrated to be effective. The need for maintaining immunosuppression (e.g. with azathioprine) after resolution has been documented. Based on clinical and radiological similarities to primary sclerosing cholangitis, cholangiocarcinoma or pancreatic neoplasm but with completely different prognosis and therapeutic strategies, it is of major importance for the physician to differentiate between these entities and AIP/IAC. Now a 68-year-old male patient was referred for a suspected tumor in the pancreatic head with consecutive jaundice. Using magnetic resonance imaging, further differentiation between chronic inflammation and a malignant process was not possible with certainty. Apart from cholestasis, laboratory studies

showed increased values for CA 19-9 to 532 U/ml (normal <37 U/ml) and hypergammaglobulinemia (immunoglobulin G, IgG) of 19 % (normal 8.0-15.8 %) with an elevation of the IgG4 subtype to 2,350 mg/L (normal 52-1,250 mg/L). Endoscopic retrograde cholangiopancreatography revealed a prominent stenosis of the distal ductus hepaticus communis caused by pancreatic head swelling and also a bihilar stenosis of the main hepatic bile ducts. Cytology demonstrated inflammatory cells without evidence of malignancy. Under suspicion of autoimmune pancreatitis with IgG4-associated cholangitis, immunosuppressive therapy with steroids and azathioprine was started. Follow-up endoscopic retrograde cholangiopancreatography after 3 months displayed regressive development of the diverse stenoses. Jaundice had disappeared and blood values had returned to normal ranges. Moreover, no tumor of the pancreatic head was present in the magnetic resonance control images. Due to clinical and radiological similarities but a consecutive completely different prognosis and therapy, it is of fundamental importance to differentiate between pancreatic cancer and autoimmune pancreatitis. Especially, determination of serum IgG4 levels and associated bile duct lesions induced by inflammation should clarify the diagnosis of autoimmune pancreatitis and legitimate immunosuppressive therapy [158].

Concomitant symptoms and diseases

With cholangitis

Autoimmune pancreatitis (AIP) is a benign disorder and a unique form of chronic pancreatitis with several characteristic features. A cystic formation that mimics a pseudocyst is a rare finding. There have been a few reports of AIP complicated by pancreatic cysts. It was presented a case of AIP with multiple pseudocysts and obstructive jaundice caused by IgG4-associated cholangitis. It was initially missed the diagnosis due to the pseudocyst. Based on the computed tomography images, laboratory findings and the therapeutic response to steroids, the case was diagnosed as AIP with pseudocysts and associated cholangiopathy [159].

Sclerosing cholangitis

American Association for the Study of Liver Diseases (AASLD) guidance recommends measurement of IgG4 in patients with sclerosing cholangitis (SC). The objective of this study was to evaluate this by analyzing our SC practice. Characteristics were collected on 168 patients with radiological or biopsy proven SC; IgG4 was measured and magnetic resonance cholangiopancreatography studies were reviewed. In all, 49 percent of patients were females and 55 percent had inflammatory bowel disease. Large duct disease was present in 63 percent, small duct disease in 8 percent, overlap with AIH in 11 percent, and secondary SC in 18 percent. Secondary etiologies included autoimmune pancreatitis (AIP) (8 %), intrahepatic cholelithiasis (3 %), portal vein thrombosis (2 %), and neonatal Kasai (2 %). In all, 101 patients had sufficient radiology and serology for re-evaluation. IgG4 was elevated (>104 mg/dl) in 22 percent of patients. This was associated with male gender (73%), a past history of pancreatitis (27 % vs 5 %), a higher alkaline phosphatase (ALP) value, median 338.5 U/I versus 160, and a higher primary sclerosing cholangitis (PSC) Mayo risk score, mean 0.6 versus -0.2. Prior biliary intervention was more likely (36 vs 13 %), while abnormal pancreatic imaging was noted in 15 percent, more frequently if IgG4 was elevated (40 vs 8 %). After excluding those with pancreatic disease on magnetic resonance imaging, 14 patients had elevated IgG4. This group had higher ALP 379 U/I versus 156, aspartate aminotransferase (AST) 72.5 U/I versus 34, alanine aminotransferase (ALT) 91 U/I versus 36, and PSC Mayo risk score values 0.4 versus -0.2. SC is a heterogeneous liver injury. IgG4 testing may be clinically important in all patients, since it appears to identify a distinct patient population, more so than just those with AIP [160].

Sclerosing sialadenitis

A new concept of IgG4-related sclerosing sialadenitis characterized by high serum IgG4 levels and tissue infiltration of IgG4-expressing plasmacytes has recently been proposed. To determine appropriate serum levels of IgG4 for monitoring disease activity, a total of 36 serum samples and eight tissue samples from patients with IgG4-related sclerosing sialadenitis were studied. The patient group consisted of six males and four females with an average age of 60 years (range, 47-74 years). Serum levels of IgG4 and the density of IgG4positive plasmacytes in affected tissues were studied. All patients had elevated serum IgG4 levels (>135 mg/dL), and IgG4-positive plasmacytes (IgG4+ plasma cells/IgG+ plasma cells >50%) were observed in the involved salivary glands. Six patients with IgG4-related sclerosing sialadenitis with high IgG4/IgG ratios and prominent infiltration of IgG4-positive plasmacytes in the involved salivary glands had systemic complications, including pancreatitis, retroperitoneal fibrosis, and/or inflammatory pseudotumor of the lung after swelling of the salivary glands. All six of these patients were successfully treated with systemic corticosteroids. In the six patients with systemic complications, treatment with systemic corticosteroids reduced the salivary gland enlargement and lowered serum IgG4 concentrations. These results suggest that IgG4 plays an important role in the pathogenesis of IgG4-related sclerosing sialadenitis, and that IgG4 levels and IgG4/IgG ratios may be used as additional indicators of disease activity and as biomarkers for potential life-threatening complications [161].

Bronchial asthma preceding IgG4-related autoimmune pancreatitis

Autoimmune pancreatitis is characterized by diffuse swelling of the pancreas and a high serum immunoglobulin (Ig) G4 concentration. Histopathologically, dense infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis are seen in the pancreas. Although allergic diseases complicating autoimmune pancreatitis have been reported, the clinical features of bronchial asthma complicated by autoimmune pancreatitis remain unclear. It was reported three cases of bronchial asthma preceding the onset of type 1 autoimmune pancreatitis by 3 months to 30 years. All three cases were males with high serum IgG, IgG4, and IgE concentrations. The radioallergosorbent tests were positive for common allergens such as mites and house dust. One case had a pulmonary manifestation that proved to be an inflammatory pseudotumor of the lung with an accumulation of IgG4-positive plasma cells. The asthma symptom was ameliorated by oral prednisolone therapy for autoimmune pancreatitis, and when the corticosteroid doses were reduced, asthma became worse in all three cases. It is possible that atopy and increased Th2 cell activity are related to a higher coincidence of IgG4-related diseases such as type 1 autoimmune pancreatitis [162].

Sjögren syndrome

Sjögren syndrome (SS) is an autoimmune disease that affects exocrine glands and therefore may affect the gastrointestinal system, from the mouth, esophagus, and bowel to the liver and pancreas. Oral involvement in SS is mainly characterized by dryness, with a wide spectrum of symptoms, from mild-to-severe xerostomia with dysgeusia and tooth decay. The dysphagia, although common, does not correlate with the reduced salivary flow rate or the dysmotility that may be present. Dyspepsia, found in up to 23 percent of patients, may be associated with gastritis, reduced acid production, and antiparietal cell antibodies, but rarely pernicious anemia. Pancreatic involvement, although rare, includes pancreatitis and pancreatic insufficiency. The most common causes of liver disease are primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic fatty liver disease, and hepatitis C virus (HCV). Although abnormal liver tests are found in up to 49 percent of patients, they are usually mild. Although sicca syndrome, abnormal histology of the salivary glands, and abnormal sialograms are common in primary biliary cirrhosis, the antibodies to Ro/SSA or La/SSB

antigens are infrequent. Xerostomia, sialadenitis, abnormal salivary flow rates, and abnormal Schirmer test in HCV vary widely among the studies, although the antibodies to Ro/SSA or La/SSB are only 1 percent. Several studies show that HCV is in saliva, although how this may impact sicca syndrome or SS in HCV is unclear. SS as a disease of exocrine glands affects many parts of the gastrointestinal system [163].

Pachymeningitis and tracheobronchial stenosis

Immunoglobulin G4 (IgG4)-related disease is a distinctive mass-forming disorder with frequent systemic involvement, most commonly in the pancreas, salivary glands and lacrimal glands. A few cases of dural involvement and one case of central airway stenosis have also been described. It was reported rare case of IgG4-related disease with intracranial hypertrophic pachymeningitis and irregular tracheobronchial stenosis. It was reviewed four previously reported cases of IgG4-related pachymeningitis. Based on the findings of the present case and those reported previously, it was discuseds the distinctive features of IgG4-related pachymeningitis [164].

Nephropathy

Nephropathy associated with IgG4-related disease is characterized by tubulointerstitial nephritis. To better identify its pathology, the present study analyzed clinicopathologic features of IgG4-related tubulointerstitial nephritis cases from across Japan. Sixteen cases were identified as IgG4-related nephropathy using the criterion of high serum IgG4 levels (>135 mg/dL) with abnormal kidney computed tomography or elevated serum creatinine levels. Male predominance (75 %) and advanced age (average, 62 years) were noted. Eight cases displayed no autoimmune pancreatitis. Renal computed tomography abnormalities were found in 12 of 13 cases examined. Renal dysfunction was found in 15 of 16 cases at biopsy. Distinctive features of tubulointerstitial lesions included (1) well-demarcated borders between involved and uninvolved areas; (2) involvement of the cortex and medulla, often extending beyond the renal capsule and with occasional extension to retroperitoneal fibrosis: (3) interstitial inflammatory cells comprising predominantly plasma cells and lymphocytes, with a high prevalence of IgG4-positive cells often admixed with fibrosis; (4) peculiar features of interstitial fibrosis resembling a "bird's-eye" pattern comprising fibrosis among inter-plasma cell spaces; and (5) deposits visible by light and immunofluorescent microscopy in the tubular basement membrane, Bowman capsule, and interstitium that are restricted to the involved portion, sparing normal parts. Ultrastructural analysis revealed the presence of myofibroblasts with intracellular/pericellular collagen accompanied by plasma cell accumulation from an early stage. Histology could not discriminate between IgG4-related tubulointerstitial nephritis with and without autoimmune pancreatitis. In conclusion, the distinctive histologic features of IgG4-related tubulointerstitial nephritis can facilitate the differential diagnosis of tubulointerstitial nephritis, even without autoimmune pancreatitis or an abnormal computed tomography suggesting a renal tumor [165].

HEREDITARY PANCREATIC DISEASES

Overview

Individuals at risk for developing hereditary cancer are offered surveillance in order to improve the prognosis. An important question is whether the benefit of surveillance outweighs the psychological burden. In this review, we evaluated all studies that investigated psychological distress and the quality of life in individuals under surveillance for hereditary cancer of the breast, ovarian, prostate, pancreas, colorectum, melanoma, and various rare syndromes such as familial adenomatous polyposis, Li-Fraumeni and Peutz-Jeghers syndrome. Thirty-two studies were identified. Surveillance for most hereditary cancers was associated with good psychological outcomes. However, surveillance of individuals at high risk for developing multiple tumors appeared to be associated with increased distress and a lower quality of life. Common factors associated with worse psychological outcomes included a personal history of cancer, female gender, having a first degree relative with cancer, negative illness perceptions and coping style. The use of a simple screening tool to identify distressed individuals is recommended [166].

Overall, genetically determined diseases of the pancreas are rare. Recently, it was demonstrated that in chronic pancreatitis many patients carry genetic changes in associated genes. Aside from chronic pancreatitis, cystic fibrosis is also characterized by exocrine insufficiency in many patients. Genetic alterations in CFTR can be found in patients suffering from chronic pancreatitis and in patients with cystic fibrosis. According to this fact, the analysis of CFTR alterations in both disease forms has improved the understanding of underlying pathogenetic mechanisms. Shwachman-Diamond and Johanson Blizzard syndrome are rare pancreatic disorders, characterized by exocrine pancreatic insufficiency in addition to other phenotypic features. As such, due to the early onset of both disease forms, diagnosis of cystic fibrosis has to be ruled out in patients with exocrine insufficiency, which can be achieved by performing sweat chloride tests. Even pancreatic cancer can accumulate in some families and a genetic basis was recently demonstrated for some patients. In all mentioned disease entities, a genetic analysis of associated genes has become essential for establishing the diagnosis. Although genetic knowledge and the finding of genetic alterations in different genes has not changed therapy of the mentioned diseases so far, the future will tell in which way genetic knowledge can be integrated to change modalities of therapy [167].

BRCA 1 and BRCA 2

The risks of cancers other than breast and ovarian amongst BRCA1 and BRCA2 mutation carriers are based on relatively few family based studies with the risk of specific cancers tested in population based samples of cancers from founder populations. We assessed risks of "other cancers" in 268 BRCA1 families and 222 BRCA2 families using a person years at risk analysis from 1975 to 2005. Cancer confirmations were overall higher than in previous family based studies at 64 percent. There was no overall increase in risk for BRCA1 carriers although oesophagus had a significant increased RR of 2.9 (95 % confidence interval 1.1 to 6.0) and stomach at 2.4 (95 % confidence interval 1.2 to 4.3), these were based mainly on unconfirmed cases. For BRCA2 increased risks for cancers of the pancreas (RR 4.1, 95 % confidence interval 1.9 to 7.8) and prostate, and uveal melanoma were confirmed. Possible new associations with oesophagus and stomach were detected but these findings should be treated with caution due to lower confirmation rates. In contrast to previous research a higher risk of prostate cancer was found in males with mutations in the BRCA2 OCCR region. The present study strengthens the known links between BRCA2 and pancreatic and prostate cancer, but throws further doubt onto any association with BRCA1. New associations with

upper gastro-intestinal malignancy need to be treated with caution and confirmed by large prospective studies [168].

Familial pancreatic cancer

Adenocarcinoma of the pancreas is a significant cause of cancer mortality, and up to 10 % of cases appear to be familial. Heritable genomic copy number variants (CNVs) can modulate gene expression and predispose to disease. Here, it was identified candidate predisposition genes for familial pancreatic cancer (FPC) by analyzing germline losses or gains present in one or more high-risk patients and absent in a large control group. A total of 120 FPC cases and 1,194 controls were genotyped on the Affymetrix 500K array, and 36 cases and 2,357 controls were genotyped on the Affymetrix 6.0 array. Detection of CNVs was performed by multiple computational algorithms and partially validated by quantitative PCR. We found no significant difference in the germline CNV profiles of cases and controls. A total of 93 non-redundant FPC-specific CNVs (53 losses and 40 gains) were identified in 50 cases, each CNV present in a single individual. FPC-specific CNVs overlapped the coding region of 88 RefSeq genes. Several of these genes have been reported to be differentially expressed and/or affected by copy number alterations in pancreatic adenocarcinoma. Further investigation in high-risk subjects may elucidate the role of one or more of these genes in genetic predisposition to pancreatic cancer [169].

Hereditary hemorrhagic telangiectasia

To analyse quantitatively and qualitatively asymptomatic hepatic and pancreatic involvement in hereditary haemorrhagic telangiectasia (HHT) using 64-section helical CT. The 64-section helical CT examinations of 19 patients with HHT (8 men, 11 women; mean age, 58 years) were quantitatively and qualitatively analysed and compared to those of 19 control subjects who were matched for age and sex. Comparisons were made using univariate analysis. Dilated and tortuous intrahepatic arterial branches was the most discriminating independent variable and had the highest specificity (100 %; 19/19) and accuracy (97 %; 37/38) for the diagnosis of HHT. Heterogeneous enhancement of hepatic parenchyma, intrahepatic telangiectases, hepatic artery to hepatic vein shunting, hepatic artery enlargement (i.e. diameter > 6.5 mm) and portal vein enlargement (i.e. diameter > 13 mm) were other variables that strongly correlated with the presence of HHT. Intrapancreatic telangiectases and arteriovenous malformations were found in 42 percent and 16 percent of patients with HHT, respectively. It was concluded that liver and pancreatic involvement in asymptomatic HHT patients is associated with myriad suggestive findings on 64-section helical CT. It can be anticipated that familiarity with these findings would result in more confident diagnosis of HHT [170].

Johanson-Blizzard syndrome

It was reported on a triplet pregnancy of consanguineous parents with one fetus being affected by recurrent Johanson-Blizzard syndrome (JBS). At autopsy in the 35th gestational week, the affected triplet presented with an especially severe and lethal manifestation of the disorder as compared to his elder affected brother and to cases in the literature, thus exemplifying great interfamilial and intrafamilial phenotypic variability. Arhinencephaly and cystic renal dysplasia associated with urethral obstruction sequence were features not described previously in the literature. In addition to the lack of exocrine acini as the characteristic feature of JBS, the pancreas revealed a resorptive inflammatory reaction with infiltration by eosinophilic granulocytes that focally dispersed onto islets of Langerhans, thus

favoring a progressive destructive rather than primary dysplastic process and possibly explaining the occurrence of diabetes mellitus in later life. JBS maps to chromosome 15q15q21.1 and is associated with mutations in the UBR1 gene. Testing the fetus and the affected sibling revealed a homozygous truncating mutation in UBR1. The resulting absence of the UBR1 protein was confirmed by Western blot. Immunohistochemical staining using a commercial anti-UBR1 antibody demonstrated staining, presumably artifactual. This finding suggests that, until an appropriately validated antibody has been identified, this modality should not be utilized for diagnosis or confirmation of this disorder [171].

Peutz-Jeghers syndrome

Duodenal intussusception is a rare entity. To date, only a few cases have been reported in the literature. In this report, a case of duodenal intussusception due to an unusual tumor was presented and the clinical features of this entity were discussed. A 42-year-old man with Peutz-Jeghers syndrome presented with epigastric pain, vomiting, and severe anemia. Computed tomography scan revealed synchronous duodenoieiunal and ieiunoieiunal intussusceptions. An emergency laparotomy revealed a polypoid mass originating from the lateral wall of the descending duodenum with intussusception of the distal duodenum. Histological examination demonstrated a poorly differentiated neuroendocrine carcinoma with muscularis infiltration, vascular invasion, and a Ki-67 index of 20 percent. A comprehensive literature search revealed 44 English reports that provided adequate descriptions of an additional 47 such cases. Clinical presentation was usually chronic and nonspecific. Diagnostic modalities included ultrasonography, upper gastrointestinal series, computed tomography, and endoscopy. Five patients were due to a non-neoplastic lesion; however, the other 43 patients were secondary to a tumor, benign in 35 cases and malignant in eight cases. Only one patient was treated by endoscopic polypectomy, whereas the remaining underwent open surgeries. Duodenal intussusception is a challenging condition due to its rarity and nonspecific presentation. It should be considered in the differential diagnosis of gastric outlet obstruction, upper gastrointestinal bleeding, pancreatitis, and obstructive jaundice [172].

STELLATE CELLS

Overview

The field of pancreatic stellate cell (PSC) biology is very young, as the essential in-vitro tools to study these cells (ie, methods to isolate and culture PSC) were only developed as recently as in 1998. Nonetheless, there has been an exponential increase in research output in this field over the past decade, with numerous research groups around the world focusing their energies into elucidating the biology and function of these cells. It is now well established that PSC are responsible for producing the stromal reaction (fibrosis) of two major diseases of the pancreas - chronic pancreatitis and pancreatic cancer. Despite exponentially increasing data, the methods for studying PSC remain variable. Although within individual laboratories methods are consistent, different methodologies used by various research groups make it difficult to compare results and conclusions. One article was not a review article on the functions of PSC. Instead, members of the Pancreatic Star Alliance (http://www.pancreaticstaralliance.com) discussed and consolidated current knowledge, to outline and delineate areas of consensus or otherwise (eq. with regard to methodological approaches) and, more importantly, to identify essential directions for future research. Pancreatic fibrosis, which develops as a consequence of chronic inflammation, leads to the loss of functional parenchyma and probably increases the risk of cancer. As the role of PSC in chronic pancreatitis and pancreatic cancer is increasingly clarified, it is anticipated that effective approaches to target PSC specifically will be developed. Such therapeutic strategies would be expected to reduce the fibrosis of chronic pancreatitis, thereby retarding the development of exocrine and endocrine insufficiency, and interrupt the interaction of PSC in the stromal reaction with pancreatic cancer cells, thereby inhibiting tumour progression and improving the otherwise dismal prognosis of this disease. Therefore, at present, the field of PSC research is dynamic and wide open, with significant potential for novel discoveries and major breakthroughs that could have a lasting impact on the treatment of patients with pancreatic diseases [173].

The interaction between pancreatic cancer cells and pancreatic stellate cells (PSCs), a major profibrogenic cell type in the pancreas, is receiving increasing attention. There is accumulating evidence that PSCs promote the progression of pancreatic cancer by increasing cancer cell proliferation and invasion as well as by protecting them from radiationand gemcitabine-induced apoptosis. Recent studies have identified that a portion of cancer cells, called "cancer stem cells", within the entire cancer tissue harbor highly tumorigenic and chemo-resistant phenotypes, which lead to the recurrence after surgery or re-growth of the tumor. The mechanisms that maintain the "stemness" of these cells remain largely unknown. We hypothesized that PSCs might enhance the cancer stem cell-like phenotypes in pancreatic cancer cells. Indirect co-culture of pancreatic cancer cells with PSCs enhanced the spheroid-forming ability of cancer cells and induced the expression of cancer stem cell-related genes ABCG2, Nestin and LIN28. In addition, co-injection of PSCs enhanced tumorigenicity of pancreatic cancer cells in vivo. These results suggested a novel role of PSCs as a part of the cancer stem cell niche [174].

Histology

Hepatic stellate cells (HSC) were first described by Karl von Kupffer in 1876; however, similar cells in the pancreas were first observed in the 1980s. In 1998, it was isolated and cultured PSC. In the normal pancreas, PSC are located in close proximity to the basal aspect of pancreatic acinar cells. In sections immunostained for the marker desmin (a cytoskeletal protein), quiescent PSC can be seen as cells with a central cell body and long cytoplasmic projections extending along the base of adjacent acinar cells similar to that of pericytes in the

mammary gland. In health, PSC exist in their quiescent phenotype and exhibit the presence of abundant vitamin A-containing lipid droplets in their cytoplasm. It is estimated that quiescent PSC form 4-7 percent of all parenchymal cells in the normal pancreas. During pancreatic injury, resident PSC transform into an activated phenotype that secretes excessive amounts of the extracellular matrix (ECM) proteins that comprise fibrous tissue. Recent evidence suggests that a small proportion of activated PSC may also be derived from circulating bone marrow (BM)-derived cells that home to the pancreas during pancreatic injury [173].

Hepatic and pancreatic stellate cells

In the human body, the stellate cell system consists of retinoid-storing cells in various organs, including the liver, pancreas, lung, kidney, intestine, spleen, adrenal gland, ductus deferens and vocal cords showing a perivascular location with a distribution typical of a pericyte. However, the origin of stellate cells is still being debated. Mesenchymal, endodermal as well as neuroectodermal origins are suggested. Neuroectoderm and mesoderm were considered as two potential origins of HSC - these cells and PSC share numerous characteristics as indicated by morphological, functional and gene expression studies. Expression profiling of PSC, HSC and fibroblasts has demonstrated that PSC and HSC are distinctly different from fibroblasts, but share many homologies including the expression of genes related to ECM proteins, contractility, retinoid metabolism (although lower retinoid content in PSC compared with HSC) and growth factors. It is therefore possible that HSC and PSC share a common origin. The origin and fate of stellate cells in the context of injury and regeneration are also a matter of ongoing debate. Regarding the contribution of BM and epithelial mesenchymal transition (EMT) of acinar cells to the PSC population, the data are limited and restricted to studies in mice. In 2006, it was reported that BM is a source of myofibroblast-like cells in fibrotic liver tissue, but the involvement of these cells in the progression of liver fibrosis remains questionable as their contribution to collagen synthesis appears to be limited. It has consistently been shown that BM-derived cells did home to the pancreas. Experimental data point to a significant but guantitatively limited contribution of BM to the pool of PSC. The effects of BM-derived and EMT-derived PSC on the course of inflammation, repair and fibrosis of the pancreas remains to be further elucidated [173].

Stem cells?

Regarding hepatic and pancreatic regeneration after injury in rodents, there is some preliminary evidence for HSC and PSC acting as stem cells in respective organs. HSC of rats express markers such as nestin and CD133, which are known to be expressed on somatic stem cells. However, before HSC can be classified as stem cells, essential characteristics of stem cells should be defined and verified in stellate cells. Briefly, stem cells are undifferentiated cells with the potential to proliferate and to undergo developmental processes. More specifically, stem cells:

- express genes required for the inhibition or induction of cell development
- maintain their characteristics in a special microenvironment (stem cell niche)
- are normally quiescent, but can be activated on demand
- proliferate/migrate when activated
- can differentiate into effector cells (plasticity) or influence the developmental fate of other cells

Through these mechanisms stem cells participate in ontogenesis, regeneration or reproduction of organisms. Furthermore, stem cells are transplantable and can survive for a long time within host tissues. First steps were made to unravel these characteristics in HSC of rodents. Genes required for stemness and developmental processes are expressed by

HSC, which preserve their quiescent state within their niche, the space of Dissé. Moreover, HSC are quiescent in normal liver, but become activated especially during stem cell-based liver repair. The gene expression of different cell types such as hepatocytes is inducible in activated HSC by cytokine treatment or co-culture with parenchymal cells, demonstrating their plasticity. In addition, some evidence exists that HSC can also contribute to liver repair. With regard to the pancreas, a recent study has described a subset of mitoxantrone (a type II topoisomerase inhibitor that disrupts DNA synthesis and DNA repair in both healthy cells and cancer cells) resistant pancreatic cells that exhibit PSC markers, and can be induced to differentiate into insulin producing beta cells when exposed to an appropriate culture medium. It is possible that PSC may also express various markers that are expressed in stem cells. However, convincing functional data showing that PSC may in fact transform into other cell types of the pancreas are not yet available. Whether PSC contribute to pancreas regeneration in a manner similar to the contribution of HSC to liver regeneration, by supporting the epithelial cells and by developing into epithelial cells, remains to be analysed [173].

Pancreatic cancer stem cells

Emerging evidence suggests that stem cells play a crucial role not only in the generation and maintenance of different tissues, but also in the development and progression of malignancies. For the many solid cancers, it has now been shown that they harbor a distinct subpopulation of cancer cells that bear stem cell features and therefore, these cells are termed cancer stem cells (CSC) or tumor-propagating cells. CSC are exclusively tumorigenic and essential drivers for tumor progression and metastasis. Moreover, it has been shown that pancreatic ductal adenocarcinoma does not only contain one homogeneous population of CSC rather than diverse subpopulations that may have evolved during tumor progression. One of these populations is called migrating CSC and can be characterized by CXCR4 coexpression. Only these cells are capable of evading the primary tumor and traveling to distant sites such as the liver as the preferred site of metastatic spread. Clinically even more important, however, is the observation that CSCs are highly resistant to chemo- and radiotherapy resulting in their relative enrichment during treatment and rapid relapse of disease. Many laboratories are now working on the further in-depth characterization of these cells, which may eventually allow for the identification of their Achilles heal and lead to novel treatment modalities for fighting this deadly disease [175].

Isolation

Isolation of quiescent PSC from rat pancreas was first reported in 1998. This method took advantage of the known vitamin A content (stored in cytoplasmic lipid droplets) of PSC, which allowed the cells to be separated by a single density gradient method using nycodenz. More recently, a similar method (albeit with some modifications) was used to isolate quiescent PSC from normal human pancreas. The gradients can be developed not only with nycodenz but also with other colloids such as percoll, iohexol, iodixanol, optiprep. The average yield of cells from a rat pancreas is approximately 3 million cells per gram of pancreas. The yield of PSC is much lower from human pancreas due to limited tissue availability and due to the higher amount of fatty tissue surrounding the resected pancreas (compared with rat pancreas), which can impede tissue digestion. PSC can also be isolated from cancerous or fibrotic human pancreas, as well as normal rat pancreas. When isolating primary cells from the pancreas, it is of vital importance to assess the purity of the cultures not only for the homogeneity of PSC but also for the absence of possible contaminants. Another confounder is the activation of PSC on plastic, which creates differences between early and late passages. Therefore, several PSC selective markers have been proposed to assess their purity and activity. The most consistent marker of PSC quiescence is the presence of vitamin A droplets in the cytoplasm. With regard to activated PSC, it is currently

not clear whether these are different from myofibroblasts of the pancreas and whether there are markers to differentiate these two cell types. However, there is strong agreement that α-SMA is not an exclusive marker for activated PSC. It is also expressed by myofibroblasts, smooth muscle cells and pericytes in blood vessels as well as the gut wall (ie, duodenum and papilla vateri). During activation, quiescent PSC lose their intracellular retinoid (vitamin A) droplets (detectable by fluorescence microscopy as a characteristic blue-green autofluorescence (rapidly fading) upon exposure to ultraviolet light at 328 nm or 350 nm) and start to express alpha-SMA. The active phenotype of PSC defined by alpha-SMA expression may have contrasting functions, e.g. profibrogenic or profibrolytic, therefore alpha-SMA is considered to be more a transdifferentiation marker indicative of a myofibroblast-like phenotype than a marker of PSC activity per se. The dynamic change in gene expression during PSC activation can be monitored by several gene products. There is some early evidence that although expressed in activated PSC, Notch3, secreted frizzled related protein 5, Wnt4 and Wnt5a are absent in quiescent PSC [173].

Activation

There is strong agreement that activation of PSC in culture can be assessed by several functional parameters. However, it is also recognised that the results of studies of PSC activation may be influenced by many different factors including stellate cell purity, culture media used and age of animals harvested or (for humans) donor age and disease (normal pancreas, chronic pancreatitis, pancreatic cancer). While the response of PSC to individual activating factors has been well characterised in vitro, researchers are also mindful that this may not reflect the true in-vivo situation in which PSC are exposed to a multiplicity of factors at any one time; there is often redundancy of the effects of cytokines; culture conditions may influence ECM composition; and isolated PSC in culture may behave differently from those in situ where they are surrounded by other cell types [173].

Stellate cells versus fibroblasts

Differentiation between PSC and pancreatic fibroblasts is an important issue given that the outgrowth method of PSC isolation involves the use of fibrotic pancreatic tissue. In contrast to pancreatic fibroblasts (PFB), PSC express alpha-SMA and form dense bodies (microfilaments) like myofibroblast-like cells. Compared with PSC, PFB are less adherent therefore detach earlier from plastic during trypsinisation. Using this difference, pure cultures of PSC and PFB can be obtained after repeated mild trypsinisation and separate cultivation. In contrast to PSC, which show a star-like shape (few are also triangular or spindle-shaped), cultured PFB are spindle-shaped and smaller. Both cell types are vimentin positive; 20-40 percent of PSC are desmin positive and more than 90 percent are alpha-SMA positive (positivity increases as cells are kept on plastic). In contrast, PFB are desmin and alpha-SMA negative. Importantly, PSC produce higher amounts of ECM proteins compared with PFB, and express the scavenger receptor CD36, CCK receptors 1/2 and ACh receptor while PFB do not express any of these receptors [173].

Species variance

There is strong agreement that there are species as well as donor-dependent variances between murine and human PSC. As a result of the limited access to human pancreatic tissue at several institutions, immortalised PSC have been proposed as an alternative model to study pancreatic stroma. Immortalised PSC may be useful for studies of molecular signalling that require manipulation of gene expression and use in in-vivo models that require cells to remain viable for a relatively longer time period. However, it is important to note that differences exist between immortalised and primary PSC, and therefore caution must be exercised when extrapolating findings with immortalised PSC to the clinical situation. Of more concern is the observation that immortalised PSC were able (albeit occasionally) to

form aggressive anaplastic tumours when injected alone into nude mice. This raises the possibility that the immortalisation procedure resulted in the preferential selection of malignant subclones. Therefore, there is strong agreement that the results of experiments obtained by using murine or immortalised PSC should ideally be verified using several different primary human PSC cultures to maximise the robustness of the data [173].

During pancreatic injuriy

Compelling evidence has accumulated in recent years to support a major role for PSC in both fibrogenesis and fibrolysis. During pancreatic injury, PSC are transformed (in response to factors that are now well identified, including oxidant stress, cytokines, growth factors and toxins such as alcohol and its metabolite acetaldehyde) from their quiescent state to an activated myofibroblast-like phenotype that synthesises and secretes excessive amounts of ECM proteins (increased fibrogenesis). Activated PSC are seen in the early phases of alcoholic chronic pancreatitis and in autoimmune pancreatitis. However, it is unclear how fibrogenesis is initiated in the inflamed pancreas. There are currently two concepts. The first concept focuses on the direct activation of PSC by acetaldehyde (the oxidative metabolite of alcohol) and oxidant stress (as shown in vitro and in animal experiments). The second concept is based on the necrosis-fibrosis sequence as the underlying pathogenic mechanisms of alcoholic chronic pancreatitis. It is proposed that the initial lesion is autodigestive tissue necrosis, which is followed by inflammation and the induction of the fibrotic reaction. In stage I with overt tissue injury, PSC are found in close association with macrophages around areas of necrosis. In stage II with extensive cellular fibrosis, PSC are found in the perilobular spaces. In stage III with established dense fibrosis in the perilobular spaces, PSC are conspicuously reduced in number, and in stage IV, when in addition to perilobular fibrosis calculi in the ducts are present, PSC are mainly detected adjacent to duct ulcerations caused by calculi. There is general agreement that in the early stages (I and II) cessation of alcohol would prevent the formation of organ fibrosis, predominantly through increased apoptosis of activated PSC. However, there is currently not enough evidence showing that increasing the fibrolytic activity of PSC reverts organised fibrosis of the pancreas [173].

Intratumorally

The tumour microenvironment is known to be an important contributor to the malignant phenotype. In the pancreas, PSC have been identified within the tumour microenvironment of pancreatic ductal adenocarcinoma. Recent evidence from animal experiments suggests that PSC can promote local tumour growth and metastatic spread and can also increase resistance to chemo and radiation treatment. The vascularity of the tumour is believed to play a role in the aggressive behaviour of pancreatic cancer. Pancreatic ductal adenocarcinoma as well as chronic pancreatitis is characterised by hypoxia and fibrosis. It remains unclear whether PSC play an overall pro-angiogenic or anti-angiogenic role in pancreatic fibrosis and cancer. PSC activity is inversely correlated with vascular density, and inhibition of stellate cell activity results in increased vascularity and the delivery of chemotherapeutic reagents. On the other hand, conditioned media of PSC induce angiogenesis both in vitro and in vivo through the production of vascular endothelial growth factor and non-vascular endothelial growth factor family members. These contradictory findings could be explained by the dynamic rather than on/off responses of PSC. It is likely that PSC may exert different effects on angiogenesis depending on the site (invading front vs dense fibrotic areas) and disease stage (early vs advanced). Pertinently, sonic hedgehog signalling has been implicated in PSC activation and suggested as an important enhancer of the desmoplastic reaction and inhibitor of stromal angiogenesis in pancreatic cancer [173].
L-cysteine

Recent studies have shown that activated pancreatic stellate cells (PSCs) play a major role in pancreatic fibrogenesis. It was aimed to study the effect of L-cysteine administration on fibrosis in chronic pancreatitis (CP) induced by trinitrobenzene sulfonic acid (TNBS) in rats and on the function of cultured PSCs. CP was induced by TNBS infusion into rat pancreatic ducts. L-cysteine was administrated for the duration of the experiment. Histological analysis and the contents of hydroxyproline were used to evaluate pancreatic damage and fibrosis. Immunohistochemical analysis of alpha-SMA in the pancreas was performed to detect the activation of PSCs in vivo. The collagen deposition related proteins and cytokines were determined by western blot analysis. DNA synthesis of cultured PSCs was evaluated by BrdU incorporation. We also evaluated the effect of L-cysteine on the cell cycle and cell activation by flow cytometry and immunocytochemistry. The expression of PDGFRbeta, TGFbetaRII, collagen 1α1 and alpha-SMA of PSCs treated with different concentrations of Lcysteine was determined by western blot. Parameters of oxidant stress were evaluated in vitro and in vivo. Nrf2, NQO1, HO-1, IL-1beta expression were evaluated in pancreas tissues by qRT-PCR. The inhibition of pancreatic fibrosis by L-cysteine was confirmed by histological observation and hydroxyproline assay. alpha-SMA, TIMP1, IL-1beta and TGF-beta1 production decreased compared with the untreated group along with an increase in MMP2 production. L-cysteine suppressed the proliferation and extracellular matrix production of PSCs through down-regulating of PDGFRbeta and TGFbetaRII. Concentrations of MDA+4-HNE were decreased by L-cysteine administration along with an increase in GSH levels both in tissues and cells. In addition, L-cysteine increased the mRNA expression of Nrf2, NQO1 and HO-1 and reduced the expression of IL-1ß in L-cysteine treated group when compared with control group. L-cysteine treatment attenuated pancreatic fibrosis in chronic pancreatitis in rats [176].

Galactin

Galectin-1 is implicated in making tumor cells immune privileged, in part by regulating the survival of infiltrating T cells. Galectin-1 is strongly expressed in activated pancreatic stellate cells (PSCs); however, whether this is linked to tumor cell immune escape in pancreatic cancer is unknown. Galectin-1 was knocked down in PSCs isolated from pancreatic tissues using small interfering RNA (siRNA), or overexpressed using recombinant lentiviruses, and the PSCs were cocultured with T cells. CD3(+), CD4(+) and CD8(+) T cell apoptosis was detected by flow cytometry; T cell IL-2, IL-4, IL-5 and INF-y production levels were quantified using ELISA. Immunohistochemical analysis showed significantly increased numbers of PSCs expressed Galectin-1 and pancreatic cancers had increased CD3(+) T cell densities compared to normal pancreas or chronic pancreatitis samples. In coculture experiments, PSCs that overexpressed Galectin-1 induced apoptosis of CD4(+) T cells and CD8(+) T cells significantly, compared to normal PSCs. Knockdown of Galectin-1 in PSCs increased CD4(+) T cell and CD8(+) T cell viability. Supernatants from T cells cocultured with PSCs that overexpressed Galectin-1 contained significantly increased levels of Th2 cytokines (IL-4 and IL-5) and decreased Th1 cytokines (IL-2 and INF-gamma). However, the knockdown of PSC Galectin-1 had the opposite effect on Th1 and Th2 cytokine secretion. The study suggests that the overexpression of Galectin-1 in PSCs induced T cell apoptosis and Th2 cytokine secretion, which may regulate PSC-dependent immunoprivilege in the pancreatic cancer microenvironment. Galectin-1 may provide a novel candidate target for pancreatic cancer immunotherapy [177].

In senescence

In chronic pancreatitis (CP), persistent activation of pancreatic stellate cells (PSC) converts wound healing into a pathological process resulting in organ fibrosis. Here, it was have analyzed senescence as a novel mechanism involved in the termination of PSC activation and tissue repair. PSC senescence was first studied in vitro by establishing long-term cultures and applying chemical triggers, using senescence-associated β-Galactosidase (SA beta-Gal) as surrogate marker. Subsequently, susceptibility of PSC to immune cell-mediated cytolysis was investigated employing cocultures. Using the model of dibutyltin dichlorideinduced CP in rats, appearance of senescent cells was monitored by immunohistochemistry and immunofluorescence, and correlated with the progression of tissue damage and repair, immune cell infiltration and fibrosis. The results indicated that long-term culture and exposure of PSC to stressors (doxorubicin, H_2O_2 and staurosporine) induced senescence. Senescent PSC highly expressed CDKN1A/p21, mdm2 and interleukin-6, but displayed low levels of α smooth muscle actin. Senescence increased the susceptibility of PSC to cytolysis. In CP, the number of senescent cells correlated with the severity of inflammation and the extension of fibrosis. Areas staining positive for SA beta-Gal overlapped with regions of fibrosis and dense infiltrates of immune cells. Furthermore, a close physical proximity of immune cells and activated PSC was observed. It was concluded that inflammation, PSC activation and cellular senescence are timely coupled processes which take place in the same microenvironment of the inflamed pancreas. Lymphocytes may play a dual-specific role in pancreatic fibrogenesis, triggering both the initiation of wound healing by activating PSC, and its completion by killing senescent stellate cells [178].

PANCREATIC CANCER

Overview

Each year pancreatic cancer is diagnosed in an estimated 43 140 patients and results in 36 800 deaths in the US. Patients are often asymptomatic, and there is currently no established method for early detection. Since 1975, the 5-year survival rate for pancreatic cancer has only improved from 2 percent to 6 percent. Only 7 percent of cases are diagnosed at an early stage, and even with disease localized to the pancreas, the 5-year survival rate is only 22 percent. At initial presentation, patients can be categorized into 3 groups:

- those with resectable disease
- those with borderline resectable disease
- those with nonresectable disease

The definition for resectable and nonresectable is generally agreed upon; however, controversy remains about the definition of borderline resectable disease, despite proposed guidelines and consensus statements. New therapeutic regimens are constantly being evaluated in an attempt to reduce the rapid progression of this disease. One strategy to improve the outcome for patients with resectable pancreatic cancer is to treat them with adjuvant chemoradiation therapy following resection. Based on promising results in early studies, the National Comprehensive Cancer Network guidelines currently recommend adjuvant chemotherapy or chemoradiation therapy for patients who underwent surgical resection and do not have evidence of recurrent or metastatic disease. Subsequent studies, however, have suggested that this approach may not be optimal, citing that approximately 25 percent of patients are unable to complete their adjuvant course or the course is prolonged because of recovery from the surgery. In patients with nonresectable disease, chemotherapy with or without radiation has been used for palliative purposes and is beneficial for some patients [179].

Although some patients receive neoadjuvant therapy in an attempt to make a nonresectable or borderline-resectable tumor resectable, more patients with resectable disease are being enrolled in clinical trials that provide neoadjuvant therapy. This means more pancreatic resections must be evaluated for therapy effect. Histologic grading schemes for the assessment of posttherapy response have been described, but difficulties associated with determining the histologic features of treatment effect in pancreatic cancer have not been addressed. To critically review the diagnostic criteria for proposed grading schemes for pancreatic cancer treated with neoadjuvant chemoradiation therapy and to provide guidance to surgical pathologists who encounter treated pancreatic cancer resections published peerreviewed literature and the personal experience of the authors were reviewed. It was concluded that assessment of treatment effect in pancreatic cancer is difficult. Pathologists need to be aware that some histologic features of treatment effect overlap with histologic features seen in untreated pancreatic cancer, such as tumor cell anaplasia, necrosis, and fibrosis. Careful assessment of pancreatic resections, including detailed gross examination and thorough histologic sampling, is important in accurately assessing treatment effect and improving patient outcomes [179].

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma discuss the workup and management of tumors of the exocrine pancreas. These NCCN Guidelines Insights provide a summary and explanation of major changes to the 2012 NCCN Guidelines for Pancreatic Adenocarcinoma. The panel made 3 significant updates to the guidelines: 1) more detail was added regarding multiphase CT techniques for diagnosis and staging of pancreatic cancer, and pancreas protocol MRI was added as an

emerging alternative to CT; 2) the use of a fluoropyrimidine plus oxaliplatin (e.g. 5-FU /leucovorin/oxaliplatin or capecitabine/oxaliplatin) was added as an acceptable chemotherapy combination for patients with advanced or metastatic disease and good performance status as a category 2B recommendation; and 3) the panel developed new recommendations concerning surgical technique and pathologic analysis and reporting [180].

Epidemiology

Pancreatic cancer mortality rates have been increasing in high-income countries between the 1950s and the 1980s, and have leveled off or declined thereafter, particularly in men. To provide a global overview of recent pancreatic cancer mortality, it was analyzed official death of the world certification data derived from the World Health Organization for 35 European countries and 19 other countries over the period 1980-2007. In 2007, the highest mortality rates from pancreatic cancer were in the Baltic countries, and some central/eastern and northern European countries (over 9.5/100 000 men and 6/100 000 women), whereas the lowest ones were in Latin America and Hong Kong (below 5/100 000 men and 3/100 000 women). Japan, the USA, Russia and the European Union (EU), as well as the largest countries in the EU, had rates around 7-9/100 000 men and 5-6/100 000 women. In the early 2000s, rates have been approximately stable in many European countries, as in the USA, Japan, and Australia. In Nordic countries and the UK, where declines in rates have been observed between the 1980s and the 1990s, mortality from pancreatic cancer has tended to rise over most recent calendar years. Some persisting rises were still found in men from a few countries of southern and central/eastern Europe (with low rates in the past), as well as in the EU overall, and in women from European and Asian countries. Recent trends were generally more favorable in young adults (30-49 years), suggesting that overall trends are likely to improve in the near future [181].

Germany

It was provided up-to-date cancer survival estimates for Germany based on data from 11 population-based cancer registries, covering 33 million people and compared them to survival estimates from the United States. Cancer patients diagnosed in 1997-2006 were included. Period analysis was employed to calculate 5-year relative survival for 38 cancers for 2002-2006. German and USA survival rates were compared utilizing the Surveillance, Epidemiology and End Results 13 database. Five-year relative survival >80 percent was observed for testicular cancer (94 %), skin melanoma (89 %), cancers of the prostate (89 %) and thyroid (88 %), Hodgkin's lymphoma (85 %) and cancers of the breast (84 %) and endometrium (81 %), which together account for almost 40 percent of cases. For the majority of cancers, German survival estimates were close to or below those in the United States. Exceptions with higher survival in Germany were cancers of the stomach, pancreas and kidney and Hodgkin's lymphoma. It was concluded that German cancer survival estimates are mostly higher than the 2000-2002 pan-European estimates. Further research is needed to investigate causes responsible for differences between German and USA cancer survival rates [182].

USA

Despite declines in incidence rates for the most common cancers, the incidence of several cancers has increased in the past decade, including cancers of the pancreas, liver, thyroid, and kidney and melanoma of the skin, as well as esophageal adenocarcinoma and certain subsites of oropharyngeal cancer associated with human papillomavirus (HPV) infection. Population-based incidence data compiled by the North American Association of Central Cancer Registries were used to examine trends in incidence rates from 1999 through 2008

for the 7 cancers listed by sex, age group, race/ethnicity, and stage at diagnosis. Joinpoint regression was used to calculate average annual percent changes in incidence rates (1999-2008). Rates for HPV-related oropharyngeal cancer, esophageal adenocarcinoma, cancer of the pancreas, and melanoma of the skin increased only in whites, except for esophageal adenocarcinoma, which also increased in Hispanic men. Liver cancer rates increased in white, black, and Hispanic men and in black women only. In contrast, incidence rates for thyroid and kidney cancers increased in all racial/ethnic groups, except American Indian/Alaska Native men. Increases in incidence rates by age were steepest for liver and HPV-related oropharyngeal cancers among those aged 54 to 64 years and for melanoma of the skin in those aged 65 years and older. Notably, for HPV-related oropharyngeal cancer in men and thyroid cancer in women, incidence rates were higher in those aged 55 to 64 years than in those aged 65 years and older. Rates increased for both local and advanced stage diseases for most cancer sites. The reasons for these increasing trends are not entirely known. Part of the increase (for esophageal adenocarcinoma and cancers of the pancreas, liver, and kidney) may be linked to the increasing prevalence of obesity as well as increases in early detection practices for some cancers. Five-year survival for pancreatic cancer was poor regardless of disease stage, and did not improve over time. Increases in pancreatic cancer incidence rates were limited to white men (0.9 % per year) and white women (1.0 % per year) during 1999 through 2008. Incidence rates also increased for men aged 55 years or older and for women of all ages as well as for local, regional, and distant staged tumors. Tobacco use (which has been declining in recent decades) and obesity (which has been increasing over time) are established risk factors; however, the causes of the observed increases in pancreatic cancer incidence rates are not known. While the prevalence of adult obesity is higher among blacks compared with whites, the isolated increases observed among whites suggests the presence of other factors resulting in increasing pancreatic cancer rates among white men and women. During 2004 through 2008, pancreatic cancer incidence rates (per 100,000 population) were highest among black men (21.3) and women (17.6) relative to white men (16.8) and women (12.8). The racial disparity in the burden of pancreatic cancer has been explained in part by increased cigarette smoking and diabetes mellitus among black men versus white men, and heavy alcohol consumption and elevated body mass index among black women versus white women. During 2000 through 2007, the 5-year survival rates were 21 percent for local stage cancer, 9 percent for regional stage cancer, and 2 percent for distant stage cancer. Avoiding tobacco use and maintaining a healthy body weight are important prevention measures for cancer of the pancreas. While no screening procedures are currently recommended at the population level, those with extremely high risks for pancreatic cancer (eg, individuals with genetic mutations associated with pancreatic cancer and/or a strong family history) may benefit from endoscopic ultrasonography or screening for the molecular markers associated with pancreatic cancer [183].

Puerto Rico

Evaluation of the extent of socioeconomic inequalities in cancer incidence and mortality is essential to generate hypotheses in population health research and provides evidence for population-based strategies for comprehensive cancer control. The objective of one study was to create an area-based socioeconomic position (SEP) index to assess possible socioeconomic disparities in incidence and mortality of selected cancers in Puerto Rico. Data for cancer incidence and mortality from 1995 to 2004 were obtained from the Puerto Rico Central Cancer Registry and the Puerto Rico Department of Health, and Puerto Rico socioeconomic data were obtained from the US Census 2000. It was used principal component and factor analysis methods to construct the SEP index at the municipality level. It was calculated age-adjusted incidence and mortality for each SEP area and used rate ratios to evaluate the differences by SEP. Incidence and mortality of cancer in Puerto Rico varied by SEP area. In general, the incidence and mortality for cancers of the esophagus and stomach were higher for municipalities with the lowest SEP; in contrast, rates for breast,

colorectal, kidney, pancreas, prostate, and thyroid were higher for areas with the highest SEP. These results highlight cancer disparities in Puerto Rico by SEP level that warrant further research [184].

Time trend regarding incidence

Hepatic, pancreatic and biliary (HPB) cancers are a group of diverse malignancies managed ideally in specialist centres. One study described recent patterns in the incidence and survival of HPB cancers in England over a ten year period (1998-2007). Data on 99,379 English patients (50,656 males; 48,723 females) diagnosed with HPB cancers between 1998 and 2007 were extracted from the National Cancer Data Repository. Data were divided into six site-specific cancer groups; pancreas, ampulla of Vater, biliary tract, primary liver, gallbladder and duodenum. Age-standardised incidence rates (per 100,000 European standard population, (ASR(E))) were calculated for each of the six groups by year of diagnosis and by socioeconomic deprivation. Survival was estimated using the Kaplan-Meier method. The largest group was pancreatic cancers (63 %), followed by primary liver (14 %) and biliary cancers (13%). ASR(E) were highest for pancreatic and primary liver cancers whereas cancers of the gallbladder, duodenum and ampulla of Vater had a very low incidence. Over time the incidence of all six groups remained relatively stable, although primary liver cancer increased slightly in males. Incidence rates were higher in males than in females in all groups except gallbladder cancer, and all six groups had a higher incidence in the more deprived quintiles. Overall survival was poor in each of the HPB cancer groups. It was concluded that HPB tumours are uncommon and are associated with poor long term survival reflecting the late stage at presentation. Incidence patterns suggest variable rates linked to socioeconomic deprivation and highlight a male predominance in all sites except the gallbladder. Identification of high risk populations should be emphasised in initiatives to raise awareness and facilitate earlier diagnosis [185].

Time trend regarding mortality

Mortality rates continue to increase for liver, esophagus, and pancreatic cancers in non-Hispanic whites and for liver cancer in non-Hispanic blacks. However, the extent to which trends vary by socioeconomic status (SES) is unknown. It was calculated age-standardized death rates for liver, esophagus, and pancreas cancers for non-Hispanic whites and non-Hispanic blacks aged 25-64 years by gender and level of education (≤12, 13-15, and ≥16 years, as a SES proxy) during 1993-2007 using mortality data from 26 states with consistent education information on death certificates. Temporal trends were evaluated using log-linear regression, and rate ratios (RRs) with 95 percent confidence intervals (CIs) compared death rates in persons with ≤ 12 versus ≥ 16 years of education. Generally, death rates increased for cancers of the liver, esophagus, and pancreas in non-Hispanic whites and non-Hispanic blacks (liver cancer only) with ≤12 and 13-15 years of education, with steeper increases in the least educated group. In contrast, rates remained stable in persons with ≥16 years of education. During 1993-2007, the RR (rates in ≤12 versus ≥16 years of education) increased for all three cancers, particularly for liver cancer among men. The recent increase in mortality rates for liver, esophagus, and pancreatic cancers in non-Hispanic whites and for liver cancer in non-Hispanic blacks reflects increases among those with lower education levels [186].

Etiological agens, risk factors and proposed risk factors

It was reviewed the current evidence for associations of several medical conditions with risk of pancreatic cancer, including allergies, pancreatitis, gall bladder disease, cholecystectomy, ulcers, gastrectomy, appendectomy, and tonsillectomy. There are consistent findings of reduced risk associated with presence of self-reported allergies, particularly hay fever but not asthma; data on other allergies are limited and inconclusive. Several studies provide evidence that patients with pancreatic cancer are more likely than comparison groups to report pancreatitis. Those studies that investigated the time between onset of pancreatitis and diagnosis of pancreatic cancer found that risk estimates declined with longer periods of time; however, increased risks were noted for long-term pancreatitis, indicating that this condition is both a risk factor and a sign of early disease. Increased risk was reported in association with cholelithiasis, but the few studies that considered time before diagnosis of cancer did not find increased risk for cholelithiasis diagnosed in the more distant past. There is weak evidence that cholecystectomy 2 or more years before cancer diagnosis is related to risk, but this is based on only a few studies. There is no consistent association between ulcers and risk, while gastrectomy may increase risk. Overall, study of these conditions, particularly those that are rare, presents methodologic challenges. Time between diagnoses is likely to be important but is not considered in most studies. Lack of adequate control in several studies for risk factors such as smoking and heavy alcohol use also makes it difficult to draw firm conclusions about these results [187].

Understanding of the etiology and identifying the risk factors are essential for the primary prevention of pancreatic cancer. Of the few potentially modifiable risk factors that have been identified, cigarette smoking, history of diabetes mellitus, and obesity seem to be among the most consistent, but the effect of dietary factors is still unclear. The aim of one study was to review of the literature examining the potential role of carbohydrates, fatty acids, meat, fruit and vegetables, alcohol. Although large prospective cohort studies with questionnaire based analyses will continue to have much to offer in defining predisposing factors for difficult diseases, such as pancreatic cancer, unfortunately dietary questionnaires do not reflect the bioavailability of the nutrients from various foods, the level of absorption from the digestive tract, or individual differences in metabolism. Greater use of participant-derived biological samples, banked plasma, germline DNA, and tumour tissue samples may help to the understanding of pancreatic cancer pathogenesis [188].

After acute pancreatitis

One study aimed to assess the risk of pancreatic cancer after acute pancreatitis using a nationwide population-based data set in Taiwan. It was conducted a retrospective cohort study of 747 patients hospitalized between 2000 and 2003 with a principal diagnosis of acute pancreatitis (the study cohort) and 5976 comparison patients. Stratified Cox proportional hazard regression adjusted for monthly income, urbanization, and geographic location of residence was used to calculate the 5-year hazard ratio (HR) of pancreatic cancer for the study versus comparison cohort. Of the total sample, 21 patients (0.31 %) developed pancreatic cancer in the 5 years after index hospitalization: 11 (1.47 %) of the study group patients and 10 (0.17 %) of the comparison group patients. After adjusting for confounders, acute pancreatitis patients were 9 times as likely as the comparison group to develop pancreatic cancer in the following 5 years (HR = 9.10; 95 % confidence interval, 3.81 to 21.76). Among patients with acute pancreatitis, the adjusted HR of pancreatic cancer was 40.03 and 3.72 times greater, respectively, for those with chronic pancreatitis and for those without than comparison patients. It was concluded that patients with acute pancreatitis have more than 9 times the risk of comparison patients to develop pancreatic cancer in the subsequent 5 years among the Hun Chinese ethnic population in Taiwan [189].

Smoking

Tobacco smoking represents an important known cause of ductal pancreatic adenocarcinoma. Recent data from pooled analyses in consortia involving multiple case-control and cohort studies suggest that heavy (but not moderate or light) alcohol

consumption also may increase pancreatic cancer risk. Animal and human evidence indicate that tobacco carcinogens and metabolites may act in concert and have both genetic and epigenetic effects at early and later stages in pancreatic tumorigenesis. One of the more important tobacco-related carcinogens, NNK, probably acts via multiple pathways. Heavy alcohol consumption may increase pancreatic cancer risk by potentiating the effects of other risk factors such as tobacco smoking, poor nutrition, and inflammatory pathways related to chronic pancreatitis, but also may have independent genetic carcinogenesis suggest multimodal, overlapping mechanistic pathways. Tobacco smoking and heavy alcohol consumption are preventable exposures, and their avoidance would substantially decrease the burden of pancreatic cancer worldwide [190].

Despite evidence that long-term smoking is the leading risk factor for pancreatic malignancies, the underlying mechanism(s) for cigarette-smoke-induced pancreatic cancer (PC) pathogenesis has not been well established. Previous studies revealed an aberrant expression of the MUC4 mucin in PC as compared with the normal pancreas, and its association with cancer progression and metastasis. Interestingly, here it was explored a potential link between MUC4 expression and smoking-mediated PC pathogenesis and report that both cigarette smoke extract and nicotine, which is the major component of CS, significantly upregulates MUC4 in PC cells. This nicotine-mediated MUC4 overexpression was via the alpha7 subunit of nicotinic acetylcholine receptor (nAChR) stimulation and subsequent activation of the JAK2/STAT3 downstream signaling cascade in cooperation with the MEK/ERK1/2 pathway: this effect was blocked by the alpha7nAChR antagonists, alphabungarotoxin and mecamylamine, and by specific siRNA-mediated STAT3 inhibition. In addition, we demonstrated that nicotine-mediated MUC4 upregulation promotes the PC cell migration through the activation of the downstream effectors, such as HER2, c-Src and FAK; this effect was attenuated by shRNA-mediated MUC4 abrogation, further implying that these nicotine-mediated pathological effects on PC cells are MUC4 dependent. Furthermore, the in vivo studies showed a marked increase in the mean pancreatic tumor weight (low dose (100 mg/m³ total suspended particulate (TSP)); high dose (247 mg/m³ TSP), and significant tumor metastasis to various distant organs in the CS-exposed mice, orthotopically implanted with luciferase-transfected PC cells, as compared with the sham controls. Moreover, the CS-exposed mice had elevated levels of serum cotinine (low dose, 156 ± 36 ng/mL; high dose, 216 ± 30 ng/mL) and increased MUC4, alpha7nAChR and pSTAT3 expression in the pancreatic tumor tissues. Altogether, the findings revealed for the first time that cigarette smoke upregulates the MUC4 mucin in PC via the alpha7nAChR/JAK2/STAT3 downstream signaling cascade, thereby promoting metastasis of pancreatic cancer [191].

Nicotine

The membrane-bound mucins are thought to play an important biological role in cell-cell and cell-matrix interactions, in cell signaling and in modulating biological properties of cancer cell. MUC4, a transmembrane mucin is overexpressed in pancreatic tumors, while remaining undetectable in the normal pancreas, thus indicating a potential role in pancreatic cancer pathogenesis. The molecular mechanisms involved in the regulation of MUC4 gene are not yet fully understood. Smoking is strongly correlated with pancreatic cancer and in the present study; we elucidate the molecular mechanisms by which nicotine as well as agents like retinoic acid (RA) and interferon-gamma (IFN-gamma) induce the expression of MUC4 in pancreatic cancer cell lines CD18, CAPAN2, AsPC1 and BxPC3. Chromatin immunoprecipitation assays and real-time PCR showed that transcription factors E2F1 and STAT1 can positively regulate MUC4 expression at the transcriptional level. IFN-gamma and RA could collaborate with nicotine in elevating the expression of MUC4, utilizing E2F1 and STAT1 transcription factors. Depletion of STAT1 or E2F1 abrogated the induction of MUC4; nicotine-mediated induction of MUC4 appeared to require alpha7-nicotinic acetylcholine receptor subunit. Further, Src and ERK family kinases also mediated the induction of MUC4, since inhibiting these signaling molecules prevented the induction of MUC4. MUC4 was also

found to be necessary for the nicotine-mediated invasion of pancreatic cancer cells, suggesting that induction of MUC4 by nicotine and other agents might contribute to the genesis and progression of pancreatic cancer. The studies show that agents that can promote the growth and invasion of pancreatic cancer cells induce the MUC4 gene through multiple pathways and this induction requires the transcriptional activity of E2F1 and STAT1. Further, the Src as well as ERK signaling pathways appear to be involved in the induction of this gene. It appears that targeting these signaling pathways might inhibit the expression of MUC4 and prevent the proliferation and invasion of pancreatic cancer cells [192].

Hepatitis B

One study was to assess the role of hepatitis B virus (HBV) infection in pancreatic ductal adenocarcinoma (PDAC) risk using a hospital-based case-control design. Patients with pathologically confirmed PDAC (n=943) and 1128 matched controls were recruited from 2 hospitals. It was evaluated the associations between risk of PDAC and age, sex, history of diabetes mellitus (DM), etc. In addition, it was examined the interactive effects of HBV status and known risk factors for pancreatic cancer. Chronic hepatitis B and inactive hepatitis B surface antigen (HBsAg) carrier state (HBsAg positive) had a significantly increased risk of pancreatic cancer, with an adjusted odds ratio of 1.60 (95 % confidence interval 1.15 to 2.24). Furthermore, significant interactions were detected between a history of DM and chronic hepatitis B and inactive HBsAg positive, but not with antibodies to hepatitis B core antigen (anti-HBc) positive/antibodies to HBsAg (anti-HBs) negative, with an adjusted odds ratio of 5.42 (95 % confidence interval 2.76 to 10.64), compared with those who were HBsAg negative/anti-HBc negative without a history of DM. These results suggest that HBsAgpositive or anti-HBc-positive/anti-HBs-negative patients have an increased risk for PDAC independent of other risk factors. Significant interactions were found between a history of DM and chronic HBV infection for PDAC risk [193].

Radiation

To assess the shape of the dose response for various cancer endpoints and modifiers by age and time a reanalysis of the US peptic ulcer data testing for heterogeneity of radiogenic risk by cancer endpoint (stomach, pancreas, lung, leukemia, all other). There are statistically significant excess risks for all cancer and for lung cancer and borderline statistically significant risks for stomach cancer, and leukemia, with excess relative risks per Gy of 0.024. 0.559, 0.042, and 1.087, respectively. There is statistically significant excess risk of pancreatic cancer when adjusted for dose-response curvature. General downward curvature is apparent in the dose response, statistically significant for all cancers, pancreatic cancer, and all other cancers (i.e. other than stomach, pancreas, lung, leukemia). There are indications of reduction in relative risk with increasing age at exposure (for all cancers, pancreatic cancer), but no evidence for guadratic variations in relative risk with age at exposure. If a linear-exponential dose response is used, there is no significant heterogeneity in the dose response among the 5 endpoints considered or in the speed of variation of relative risk with age at exposure. The risks are generally consistent with those observed in the Japanese atomic bomb survivors and in groups of nuclear workers. It was concluded that there are excess risks for various malignancies in this data set. Generally there is a marked downward curvature in the dose response and significant reduction in relative risk with increasing age at exposure. The consistency of risks with those observed in the Japanese atomic bomb survivors and in groups of nuclear workers implies that there may be little sparing effect of fractionation of dose or low-dose-rate exposure [194].

Atomic bomb survivors

This is the 14th report in a series of periodic general reports on mortality in the Life Span Study (LSS) cohort of atomic bomb survivors followed by the Radiation Effects Research

Foundation to investigate the late health effects of the radiation from the atomic bombs. During the period 1950-2003, 58% of the 86,611 LSS cohort members with DS02 dose estimates have died. The 6 years of additional follow-up since the previous report provide substantially more information at longer periods after radiation exposure (17 % more cancer deaths), especially among those under age 10 at exposure (58 % more deaths). Poisson regression methods were used to investigate the magnitude of the radiation-associated risks. the shape of the dose response, and effect modification by gender, age at exposure, and attained age. The risk of all causes of death was positively associated with radiation dose. Importantly, for solid cancers the additive radiation risk (i.e., excess cancer cases per 10(4) person-years per Gy) continues to increase throughout life with a linear dose-response relationship. The sex-averaged excess relative risk per Gy was 0.42 for all solid cancer at age 70 years after exposure at age 30 based on a linear model. The risk increased by about 29 percent per decade decrease in age at exposure. The estimated lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy, and a formal dose-threshold analysis indicated no threshold; i.e. zero dose was the best estimate of the threshold. The risk of cancer mortality increased significantly for most major sites, including stomach, lung, liver, colon, breast, gallbladder, esophagus, bladder and ovary, whereas rectum, pancreas, uterus, prostate and kidney parenchyma did not have significantly increased risks. An increased risk of non-neoplastic diseases including the circulatory, respiratory and digestive systems was observed, but whether these are causal relationships requires further investigation. There was no evidence of a radiation effect for infectious or external causes of death [195].

Cruciferous vegetables (cabbage)

Cruciferous vegetables have been suggested to protect against various cancers, though the issue is open to discussion. To further understand their role, it was analyzed data from a network of case-control studies conducted in Italy and Switzerland. The studies included a total of 1468 cancers of the oral cavity/pharynx, 505 of the esophagus, 230 of the stomach, 2390 of the colorectum, 185 of the liver, 326 of the pancreas, 852 of the larynx, 3034 of the breast, 367 of the endometrium, 1031 of the ovary, 1294 of the prostate, 767 of the kidney, and 11 492 controls. All cancers were incident, histologically confirmed; controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute nonneoplastic conditions. The multivariate odds ratio (OR) for consumption of cruciferous vegetables at least once a week as compared with no/occasional consumption was significantly reduced for cancer of the oral cavity/pharynx, esophagus, colorectum, breast, and kidney. The OR was below unity, but not significant, for stomach, liver, pancreatic (OR 0.90), laryngeal, endometrial, ovarian, and prostate cancer [196].

Red meat

Whether red and processed meat consumption is a risk factor for pancreatic cancer remains unclear. It was conducted a meta-analysis to summarise the evidence from prospective studies of red and processed meat consumption and pancreatic cancer risk. Relevant studies were identified by searching PubMed and EMBASE databases through November 2011. Study-specific results were pooled using a random-effects model. Eleven prospective studies, with 6643 pancreatic cancer cases, were included in the meta-analysis. An increase in red meat consumption of 120 g per day was associated with an overall relative risk (RR) of 1.13 (95 % confidence interval 0.93 to 1.39). Red meat consumption was positively associated with pancreatic cancer risk in men (RR 1.29), but not in women (RR 0.93). The RR of pancreatic cancer for a 50 g per day increase in processed meat consumption was 1.19. Findings from this meta-analysis indicate that processed meat consumption is positively associated with pancreatic cancer risk. Red meat consumption was associated with an increased risk of pancreatic cancer in men [197].

Heterocyclic amines

Epidemiological studies report positive associations between high-temperature cooked meat intake and pancreatic cancer. It was assessed associations between dietary intake of heterocyclic amines (HCAs) and benzo(a)pyrene (BaP)-mutagens formed in meat cooked at high temperatures-and incident exocrine pancreatic cancer in a prospective cohort. The 62581 subjects randomized to screening in the Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO) who completed an initial dietary survey that assessed meat intake, cooking methods, and doneness preferences defined the cohort. Subjects were surveyed annually for incident cancers through 2007. A National Cancer Institute research database (CHARRED) was used to estimate HCA and BaP intake and a Mutagenic Activity Index (MAI) from survey data. Proportional hazard ratios (HRs) for risk of pancreatic cancer were estimated from multi-variate Cox regression models by quintile of intake, with the lowest quintile as the referent. During follow-up (median: 10 yr), 248 cases of exocrine pancreatic cancer were confirmed. Preferences for well and very well done meat were generally associated with increased risks. Significant elevations in pancreatic cancer risk were found in upper quintiles of MAI, and individual mutagens 2-amino-3,4,8-trimethylimidazo[4,5and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline f]quinoxaline (DiMelQx) (MelQx). Compared to the lowest quintile of MAI, the third and fifth quintiles brought HRs of 1.86 and 1.87, respectively. These three exposures exhibited significant positive trends in risk as their levels increased. Consuming well-done meat cooked at high temperatures, which contains high mutagen levels, appears to confer increased risk of pancreatic cancer [198].

Polycyclic aromatic hydrocarbons

Several occupational exposures have been linked to excess risk of pancreatic cancer; however, most associations are not well established. The objective of one review article was to report on the more recently published studies (1998-2010), and provide a summary of the most consistently reported occupational risk factors for pancreatic cancer, including exposure to chlorinated hydrocarbon compounds, pesticides, polycyclic aromatic hydrocarbons (PAHs), metals, nitrosamines, radiation, various airborne particles, and employment in sedentary occupations. It was concluded that the strongest and most consistent findings linking occupational exposures with pancreatic cancer risk to date are for chlorinated hydrocarbons and PAHs [199].

Physical activity

Numerous epidemiologic studies have demonstrated that regular physical activity convincingly reduces risk for colon cancer, probably for endometrium and postmenopausal breast cancer, and possibly for premenopausal breast, prostate, lung, and pancreas cancer. Relative risk reductions range from 10-30 percent. On the absolute scale about 9-19 percent of the most frequent cancers can be attributed to a lack of sufficient physical activity. Thus, exercise, as a modifiable health behavior, has a strong potential for primary cancer prevention. Current recommendations call for at least 30-60 min of moderate to vigorous activity daily. Physical activity is also increasingly gaining importance in cancer treatment and is now considered to be feasible, safe, and even recommended in almost all stages of disease. Randomized-controlled trials show that disease- and treatment-related symptoms, such as fatigue, sleep disorders, and depression which sometimes limit quality of life in cancer patients over years, can be reduced by physical activity. For disease-specific and total mortality, clinical studies are not yet available. However, preliminary observational studies with breast, colon, and prostate cancer patients show risk reductions [200].

Obesity

During the past decade, skeletal muscle has been identified as a secretory organ. Accordingly, we have suggested that cytokines and other peptides that are produced. expressed and released by muscle fibres and exert either autocrine, paracrine or endocrine effects should be classified as myokines. The finding that the muscle secretome consists of several hundred secreted peptides provides a conceptual basis and a whole new paradigm for understanding how muscles communicate with other organs, such as adipose tissue, liver, pancreas, bones and brain. However, some myokines exert their effects within the muscle itself. Thus, myostatin, LIF, IL-6 and IL-7 are involved in muscle hypertrophy and myogenesis, whereas BDNF and IL-6 are involved in AMPK-mediated fat oxidation. IL-6 also appears to have systemic effects on the liver, adipose tissue and the immune system, and mediates crosstalk between intestinal L cells and pancreatic islets. Other myokines include the osteogenic factors IGF-1 and FGF-2; FSTL-1, which improves the endothelial function of the vascular system; and the PGC-1α-dependent myokine irisin, which drives brown-fat-like development. Studies in the past few years suggest the existence of yet unidentified factors. secreted from muscle cells, which may influence cancer cell growth and pancreas function. Many proteins produced by skeletal muscle are dependent upon contraction; therefore, physical inactivity probably leads to an altered myokine response, which could provide a potential mechanism for the association between sedentary behaviour and many chronic diseases [201].

In the United States, pancreatic cancer is characterized by a low 5-year survival rate of approximately 6 percent, fewer than 10 percent of patients diagnosed with localized disease and thus candidates for "curative" surgical resection, increasing incidence and few established risk factors. Similar statistics are observed for other industrialized nations. With new evidence to suggest that pancreatic cancer develops over a number of years, markers that can better identify high risk patients and are applicable to earlier diagnosis hold promise for improving these dire statistics. Obesity is one of the few modifiable risk factors that has been associated with increased risk of pancreatic cancer and also is related to increased risk of diabetes, a condition that in turn has been associated with pancreatic cancer development. Given recent data that nearly 70 percent of United States adults are overweight or obese, a clarification of the complex association between obesity and pancreatic cancer may disclose targets for prevention and intervention to decrease incidence and improve prognosis of this highly fatal disease. An overview of the current epidemiology and hypothesized biological mechanisms involved in the obesity-pancreatic cancer association were presented [202].

Annual updates on cancer occurrence and trends in the United States are provided through collaboration between the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR). 2012 year's report highlights the increased cancer risk associated with excess weight (overweight or obesity) and lack of sufficient physical activity (<150 minutes of physical activity per week). Data on cancer incidence were obtained from the CDC, NCI, and NAACCR; data on cancer deaths were obtained from the CDC's National Center for Health Statistics. Annual percent changes in incidence and death rates (age-standardized to the 2000 US population) for all cancers combined and for the leading cancers among men and among women were estimated by joinpoint analysis of long-term trends (incidence for 1992-2008 and mortality for 1975-2008) and short-term trends (1999-2008). Information was obtained from national surveys about the proportion of US children, adolescents, and adults who are overweight, obese, insufficiently physically active, or physically inactive. Death rates from all cancers combined decreased from 1999 to 2008, continuing a decline that began in the early 1990s, among men and among women in most racial and ethnic groups. Death rates decreased from 1999 to 2008 for most cancer sites, including the 4 most common cancers (lung, colorectum,

breast, and prostate). The incidence of prostate and colorectal cancers also decreased from 1999 to 2008. Lung cancer incidence declined from 1999 to 2008 among men and from 2004 to 2008 among women. Breast cancer incidence decreased from 1999 to 2004 but was stable from 2004 to 2008. Incidence increased for several cancers, including pancreas, which are associated with excess weight. It was concluded that although improvements are reported in the US cancer burden, excess weight and lack of sufficient physical activity contribute to the increased incidence of many cancers, adversely affect quality of life for cancer survivors, and may worsen prognosis for several cancers. The current report highlights the importance of efforts to promote healthy weight and sufficient physical activity in reducing the cancer burden in the United States [203].

In China

The objective was to provide an evidence-based, systematic assessment of the burden of cancer due to overweight/obesity and physical inactivity in China. One study evaluated the proportion of cancers of colon, rectum, pancreas, breast (postmenopausal), endometrium, and kidney attributable to overweight (30 kg/m² > body mass index (BMI) \ge 25 kg/m²/obesity $(BMI \ge 30 \text{ kg/m}^2)$ and physical inactivity in China in 2005. Data of prevalence of overweight/obesity and lack of physical activity were derived from cross-sectional surveys among representative samples of Chinese population, and data of relative risks on cancers were derived from meta-analyses or large-scale studies from China and East Asian populations. The attributable fractions were calculated by combining both data of prevalence and relative risks. In China in 2005, 0.32 percent of cancer deaths and 0.65 percent of cancer cases were attributable to overweight and obesity combined. Lack of physical activity was responsible for 0.27 percent of cancer deaths and 0.39 percent of cancer cases. Future projections indicate that the contribution of overweight and obesity to the overall cancer burden will increase in the next decades. The largest increased attributable fractions will be for endometrial cancer. The increase in attributable fractions would be greater in men and in rural populations. Although the current burden of cancer associated with overweight/obesity and physical inactivity is still relatively small in China, it is expected to increase in the future [204].

Cholesterol

One study assesses the association between dietary cholesterol intake and the risk of various cancers. Mailed questionnaires were completed between 1994 and 1997 in eight Canadian provinces by 1182 incident histologically confirmed cases of the stomach, 1727 of the colon, 1447 of the rectum, 628 of the pancreas, 3341 of the lung, 2362 of the breast, 442 of the ovary, 1799 of the prostate, 686 of the testis, 1345 of the kidney, 1029 of the bladder, 1009 of the brain, 1666 non-Hodgkin's lymphomas (NHL), 1069 leukemia and 5039 population controls. Information on dietary habits and nutrition intake were obtained using a food frequency questionnaire, which provided data on eating habits 2 years before the study. Odds ratios (ORs) were derived by unconditional logistic regression to adjust for total energy intake and other potential confounding factors. Dietary cholesterol was positively associated with the risk of cancers of the stomach, colon, rectum, pancreas, lung, breast (mainly postmenopausal), kidney, bladder and NHL: the ORs for the highest versus the lowest quartile ranged from 1.4 to 1.7. In contrast, cholesterol intake was inversely associated with prostate cancer. The findings add to the evidence that high cholesterol intake is linked to increased risk of various cancers. A diet low in cholesterol may play a role in the prevention of several cancers [205].

Diabetes

One study aimed to investigate whether the reported relationship between diabetes and pancreatic cancer (PC) could result from detection bias and whether dyslipidemia and/or

new-onset diabetes (diagnosed within 1 year) could predict PC. A random sample of 1 million subjects covered by National Health Insurance was recruited. From 2003 to 2005, 495,493 men and 503,901 women without PC were followed up. Cox regression was used to evaluate the adjusted relative risk considering potential PC detection examinations and covariates. Diabetic patients had a significantly higher probability of receiving examinations that might lead to PC diagnosis. In Cox proportional hazards regression models, diabetes was not a significant predictor, but dyslipidemia was significantly associated with an approximately 40 percent higher risk of PC. Age, living in more urbanized regions, and potential PC detection examinations were significant covariates. Patients with new-onset diabetes and previous dyslipidemia had a remarkably higher risk compared with those without either condition (relative risk 2.51, 95 % confidence interval 1.17 to 5.40). It was thus concluded that dyslipidemia, but not diabetes, is a significant risk factor for PC. The link between diabetes and PC is likely due to confounders and detection bias. Patients with new-onset diabetes and a history of dyslipidemia are at an especially high risk of PC [206].

While diabetes has been linked to several cancers in the gastrointestinal (GI) tract, findings have been mixed for sites other than colorectal and liver cancer. We used the Women's Health Initiative (WHI) data and conducted a comprehensive assessment of associations between diabetes and GI malignancy (esophagus, stomach, liver, biliary, pancreas, colon, and rectal). A total of 145,765 postmenopausal women aged 50-79 enrolled in the WHI were followed for a mean 10 years. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) for the association between GI cancers and diagnosed diabetes, including its duration and treatment. Diabetes at enrollment was associated with increased risk of liver (HR 2.97), pancreatic (HR 1.62; 95 % confidence interval 1.15 to 2.30), colon (HR 1.38), and rectal (HR 1.87) cancer. Diabetes severity, assessed by duration or need for pharmacotherapy, appeared to have stronger links to risk of liver, pancreatic, and rectal cancer, but not colon cancer. There was no statistically significant association of diabetes with biliary, esophageal, and stomach cancers. Type 2 diabetes is associated with a significantly increased risk of cancers of the liver, pancreas, colon, and rectum in postmenopausal women. The suggestion that diabetes severity further increases these cancer risks requires future studies [207].

Diabetes has been associated to the risk of a few cancer sites, though quantification of this association in various populations remains open to discussion. It was analyzed the relation between diabetes and the risk of various cancers in an integrated series of case-control studies conducted in Italy and Switzerland between 1991 and 2009. The studies included 1,468 oral and pharyngeal, 505 esophageal, 230 gastric, 2,390 colorectal, 185 liver, 326 pancreatic, 852 laryngeal, 3,034 breast, 607 endometrial, 1,031 ovarian, 1,294 prostate, and 767 renal cell cancer cases and 12,060 hospital controls. The multivariate odds ratios (OR) for subjects with diabetes as compared to those without-adjusted for major identified confounding factors for the cancers considered through logistic regression models-were significantly elevated for cancers of the oral cavity/pharynx, esophagus, colorectum, liver, pancreas (OR 3.3), postmenopausal breast, and endometrium. For cancers of the oral cavity, esophagus, colorectum, liver, and postmenopausal breast, the excess risk persisted over 10 years since diagnosis of diabetes. The data confirm and further quantify the association of diabetes with colorectal, liver, pancreatic, postmenopausal breast, and endometrial cancer and suggest for the first time that diabetes may also increase the risk of oral/pharyngeal and esophageal cancer [208].

Type 2 diabetes mellitus is likely the third modifiable risk factor for pancreatic cancer after cigarette smoking and obesity. Epidemiological investigations have found that long-term type 2 diabetes mellitus is associated with a 1.5-fold to 2.0-fold increase in the risk of pancreatic cancer. A causal relationship between diabetes and pancreatic cancer is also supported by findings from prediagnostic evaluations of glucose and insulin levels in prospective studies. Insulin resistance and associated hyperglycemia, hyperinsulinemia, and inflammation have

been suggested to be the underlying mechanisms contributing to development of diabetesassociated pancreatic cancer. Signaling pathways that regulate the metabolic process also play important roles in cell proliferation and tumor growth. Use of the antidiabetic drug metformin has been associated with reduced risk of pancreatic cancer in diabetics and recognized as an antitumor agent with the potential to prevent and treat this cancer. On the other hand, new-onset diabetes may indicate subclinical pancreatic cancer, and patients with new-onset diabetes may constitute a population in whom pancreatic cancer can be detected early. Biomarkers that help define high-risk individuals for clinical screening for pancreatic cancer are urgently needed. Why pancreatic cancer causes diabetes and how diabetes affects the clinical outcome of pancreatic cancer have yet to be fully determined. Improved understanding of the pathological mechanisms shared by diabetes and pancreatic cancer would be the key to the development of novel preventive and therapeutic strategies for this cancer [209].

Genetics

Type 2 diabetes is associated with increased pancreatic cancer risk; however, the nature of this relationship is not clear. It was examined the link between 10 diabetes-related single-nucleotide polymorphisms and pancreatic cancer in a case-control study conducted in 1994 to 1998. Cases (n=162) were ascertained from hospitals. Controls (n=540) from the general population were frequency matched by age, gender, and race. Unconditional logistic regression provided odds ratios of pancreatic cancer and 95 percent confidence intervals. In a multivariate-adjusted model, a significant association was observed only for rs780094 in the glucokinase regulator (GCKR) gene: odds ratios for pancreatic cancer were 1.00 for TT, 1.35 for CT, and 2.14 for CC genotypes and did not change after the adjustment for diabetes. This study provides the first evidence that GCKR rs780094, a single-nucleotide polymorphism related to diabetes, may be associated with pancreatic cancer risk. Although the results from this analysis are preliminary, there is a biologic plausibility for such an association [210].

Role for metastases

As a vital step in the progression of cancer, metastasis poses the largest problem in cancer treatment and is the main cause of death of cancer patients. In pancreatic cancer, almost 80 percent of patients have locally deteriorated or metastatic disease and thus are not appropriate for resection at the time of diagnosis. Due to the high rate of incidence and mortality, it is crucial to study the molecular mechanisms of metastasis to clarify therapeutic targets to hinder the spread of cancer. Diabetes mellitus has long been considered a potential risk factor for pancreatic cancer. In one review, it was comprehensively described the role of hyperglycemia in governing critical steps of the metastatic process. In particular, it was focused on the hyperglycemia-dependent aspects of the Epithelial-Mesenchymal Transition (EMT) and vascular dysfunction. Furthermore, we discuss how hyperglycemia-related production of reactive oxygen species (ROS) may play an important role in these two processes. A deep understanding of metastasis mechanisms will identify novel targets for therapeutic intervention [211].

IGF-1

Insulin-like growth factors (IGFs) and their binding proteins (BPs) regulate cell differentiation, proliferation and apoptosis, and may have a role in the aetiology of various cancers. Information on their role in pancreatic cancer is limited and was examined here in a casecontrol study nested within the European Prospective Investigation into Cancer and Nutrition. Serum concentrations of IGF-I and IGFBP-3 were measured using enzyme-linked immunosorbent assays in 422 cases and 422 controls matched on age, sex, study centre, recruitment date, and time since last meal. Conditional logistic regression was used to compute odds ratios (OR) and 95 percent confidence intervals (CI) adjusted for confounding variables. Neither circulating levels of IGF-I (OR=1.21), IGFBP-3 (OR=1.00), nor the molar IGF-I/IGFBP-3 ratio, an indicator of free IGF-I level (OR=1.22), were statistically significantly associated with the risk of pancreatic cancer. In a cross-classification, however, a high concentration of IGF-I with concurrently low levels of IGFBP-3 was related to an increased risk of pancreatic cancer (OR=1.72). On the basis of these results, circulating levels of components of the IGF axis do not appear to be the risk factors for pancreatic cancer. However, on the basis of the results of a subanalysis, it cannot be excluded that a relatively large amount of IGF-1 together with very low levels of IGFBP-3 might still be associated with an increase in pancreatic cancer risk [212].

Proton pump inhibitor

The relationship between use of proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H₂RAs) and pancreatic cancer risk has yet to be examined. Data from a range of studies suggest biologically plausible mechanisms, whereby these drugs (or the conditions for which they are prescribed) may affect pancreatic cancer risk. The objective of this study was to investigate the relationship between use of PPIs/ H₂RAs and pancreatic cancer risk. A nested case-control study was conducted within the UK general practice research database. Cases had a diagnosis of exocrine pancreatic cancer and controls were matched to cases on general practice site, sex and year of birth. Exposure to PPIs and to H₂RAs since entry into the database until 2 years before the diagnosis date (corresponding date in controls) and in the 5 years before the diagnosis date were separately assessed. Ever use of PPIs since entry into the database (excluding the 2 years prior to diagnosis) was not associated with risk of pancreatic cancer; OR 1.02. Neither the dose nor the duration of PPI or H₂RAs use was associated with pancreatic cancer risk. No consistent patterns of association were seen when cumulative exposure (dose and duration) to these drugs was examined separately or together [213].

Vitamin D

Exocrine pancreatic insufficiency due to chronic pancreatitis may result – depending on the degree of insufficiency - in a decrease in serum 25-hydroxyvitamin D (25(OH)D) level. However, the data in the literature concerning the rate and extent of vitamin D deficiency in pancreatic cancer with or without previous pancreas resection, are very rare, in particular regarding the question how to supplement these patients with vitamin D. In recent years, vitamin D is increasingly being discussed as one factor involved not only in musculo-skeletal diseases but also in cardiovascular and autoimmune diseases, cancer development, diabetes mellitus and overall mortality. In all, 248 ambulatory patients (n=140 patients suffering from exocrine pancreatic insufficiency due to chronic pancreatitis, pancreatic cancer with/without previous resections of the pancreas n=108 patients without pancreatic disease). we measured the serum 25(OH)D concentrations by the chemoluminescence method. In addition, in 91 of these patients (n=65 pancreatic patients, n=26 controls), it was started supplementation with oral vitamin D in combination with dietary advice and adequate substitution with pancreatic enzyme preparations, followed by subsequent serum 25(OH)D determinations. The oral vitamin D doses varied from 1000 IU per day over 1x 20,000 IU per week, or 2-3 times 20,000 IU per week up to 20,000 IU per day in single patients, depending on the underlying disease and the estimated degree of maldigestion/malassimilation. In addition, in a pilot trial vitamins A and E were measured in the serum from 121 and 105 of these patients respectively (HPLC method). Serum 25(OH)D concentrations were <30 ng/mL in 93 percent of the patients with pancreatic diseases,<20 ng/mL in 78 percent, <10 ng/mL in 32 percent and <4 ng/mL in 9 percent. The results were comparable to those in patients suffering from chronic pancreatitis and those with pancreatic tumor disease, with or without a previous tumor resection (n=51 Whipple procedure, n=11 left resection, n=9 total duodenopancreatectomy). Similar data were also found in the controls, only slightly higher. In contrast to the vitamin D data, however, determination of vitamins A and E in the serum resulted in values within the normal range for the majority of the patients of both groups, suggesting a diminished vitamin D uptake as being at least one reason to explain the low serum vitamin D concentrations in the patients with pancreatic diseases. Individual supplementation with oral vitamin D in all patients studied (n=91) resulted in an increase of the serum 25(OH)D concentrations into the normal range. The data of a subgroup of patients with continuous long-term supplementation, however, suggest that some patients with pancreatic diseases may need a significantly higher vitamin D supplementation, up to 20000 IU per day in single patients, compared to the controls. The results demonstrate that vitamin D deficiency is a common problem in patients suffering from exocrine pancreatic insufficiency from various reasons as well as in our controls. Apart from insufficient sun exposure, exocrine pancreatic insufficiency, as well as a too low vitamin D uptake with food seem to represent the main causes of low serum 25(OH)D. In nearly all patients, the serum 25(OH)D concentrations could be normalized by oral supplementation of vitamin D in the case of individual therapy based on routine serum controls [214].

Laboratory studies suggest that vitamin D may inhibit pancreatic cancer cell growth. However, epidemiologic studies of vitamin D and pancreatic cancer risk have been conflicting. To determine whether prediagnostic levels of plasma 25-hydroxyvitamin D (enzyme immunoassay) were associated with risk of pancreatic cancer, it was conducted a pooled analysis of nested case-control studies with 451 cases and 1,167 controls from five cohorts through 2008. Median follow-up among controls was 14. years in Health Professionals Follow-Up Study (HPFS), 18 years in Nurses' Health Study (NHS), 25 years in Physicians' Health Study (PHS), 12 years in Women's Health Initiative-Observational Study (WHI), and 14 years in Women's Health Study (WHS). Logistic regression was used to compare the odds of pancreatic cancer by plasma level of 25(OH)D. Mean plasma 25(OH)D was lower in cases versus controls (61 vs 65 nmol/L). In logistic regression models, plasma 25(OH)D was inversely associated with odds of pancreatic cancer. Participants in quintiles two through five had multivariable-adjusted ORs (95 % confidence intervals) of 0.79 (0.56 to 1.10), 0.75 (0.53 to 1.06), 0.68 (0.48 to 0.97), and 0.67 (0.46 to 0.97; respectively, compared with the bottom quintile. Compared with those with insufficient levels (25[OH]D, <50 nmol/L), ORs were 0.75 for subjects with relative insufficiency (<75 nmol/L) and 0.71 for those with sufficient levels (≥ 75 nmol/L). No increased risk was noted in subjects with 25(OH)D ≥100 nmol/L, as suggested in a prior study. In subgroup analyses, ORs for the top versus bottom quartile were 0.72 for women, 0.73 for men, and 0.73 for Whites. Among participants in five large prospective cohorts, higher plasma levels of 25(OH)D were associated with a lower risk for pancreatic cancer [215]

Although potentially modifiable risk factors for pancreatic cancer include smoking, obesity, and diabetes, less is known about the extent to which diet affects cancer risk. Recent studies have demonstrated some consistency for dietary fat being associated with elevated pancreatic cancer risk, particularly from animal sources. However, less is known about which fatty acids pose the greatest risk. Vitamin D, due to its endogenous production following UV-B exposure, is a unique risk factor in that researchers have created several methods to assess its exposure in humans. Studies that measured vitamin D exposure differently have shown inconsistent results. Dietary studies suggest protective associations, whereas studies of circulating 25-hydroxyvitamin D status show null or positive associations with low or very high concentrations, respectively. Several, but not all epidemiologic studies provide evidence of an inverse relationship between total and/or dietary folate and risk of pancreatic cancer. Protective associations for circulating folate are more often observed among populations with inadequate status. This article reviews the current epidemiological and experimental evidence investigating the relationship of dietary fat, vitamin D, and folate with pancreatic cancer. Additionally the mechanisms by which these risk factors may contribute to cancer, the methodological challenges involved with assessing risk, and other obstacles encountered when ascertaining the magnitude and direction of these three exposures are discussed [216].

High concentrations of circulating 25-hydroxyvitamin D [25(OH)D] have been associated with elevated pancreatic cancer risk. As this is contrary to an expected inverse association between vitamin D status and cancer, we examined whether vitamin D binding protein (DBP), the primary carrier of vitamin D compounds in circulation, plays a role in this relationship. Prediagnostic serum DBP and 25(OH)D were studied in relation to risk of pancreatic cancer in a nested case-control study of 234 cases and 234 controls in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish men. ORs and 95 percent confidence intervals were estimated using logistic regression, and statistical tests were twosided. It was found that DBP and 25(OH)D were correlated, and DBP was inversely associated with pancreatic cancer risk (OR 0.66, for the highest vs lowest quartile). Importantly, this association seemed to have a threshold between quartiles 2 to 4 and quartile 1, and was primarily evident among men with concurrent high 25(OH)D concentrations (OR 0.33, for highest vs lowest quartile), with no association in men with lower serum 25(OH)D (OR 1.28, for highest vs lowest quartile). Men with higher 25(OH)D concentrations and serum DBP below the median showed greatly elevated risk of pancreatic cancer (OR 5.01, for highest vs lowest quartile), while risk was weakly inversely associated with serum 25(OH)D when DBP concentrations were higher. Taken together, the findings indicate that higher DBP concentrations may sequester more 25(OH)D and reduce free 25(OH)D bioavailability. Simultaneous examination of DBP and 25(OH)D may be important in determining the association of vitamin D with cancer risk [217].

Vitamin C and E

Epidemiological data investigating the relation between fruit and vegetable consumption and pancreatic cancer risk have shown inconsistent results so far. Most case-control studies observed an inverse association with total fruit and vegetable consumption, whereas results from most cohort studies have largely been null. It was examined prospectively the relation between pancreatic cancer risk and intake of vegetables, fruits, carotenoids and vitamins C and E. The Netherlands Cohort Study consisted of 120,852 men and women who completed a questionnaire at baseline in 1986, including a validated 150-item food-frequency questionnaire. After 16.3 years of follow-up, 423 cases were available for analysis. Total vegetable and total fruit consumption were not associated with pancreatic cancer risk (highest vs. lowest quintile, multivariable-adjusted hazard rate ratio 1.23, 95 % confidence interval: 0.86 to 1.75 and multivariable-adjusted hazard rate ratio 0.90, 95 % confidence interval: 0.66 to 1.24, respectively). Also, for cooked vegetables, raw vegetables and vegetables and fruits classified into subgroups, no associations were observed. Dietary carotenoids, vitamin C and E intake and supplements containing vitamin C or E were not associated with pancreatic cancer risk. The results were not modified by gender, smoking status and body mass index. In conclusion, it was observed no association between a high consumption of vegetables and fruits and pancreatic cancer risk in this large cohort study. which is in agreement with previous prospective studies. Furthermore, it was observed no association between the intake of carotenoids, vitamins and vitamin supplements and pancreatic cancer risk [218].

Cadmium

One study examined prospective data from the Third National Health and Nutrition Examination Survey (NHANES III) cohort to investigate the relationship between cadmium exposure and cancer mortality, and the specific cancers associated with cadmium exposure, in the general population. Vital status and cause of death through 2006 were obtained by the National Center for Health Statistics for NHANES III participants. The cadmium concentration of spot urine samples was measured and corrected for urine creatinine (uCd). Weighted Cox proportional hazards regression with age as the time metric was applied to estimate sex-

specific adjusted HRs (aHRs) of mortality associated with uCd for all cancers and the cancers responsible for the most deaths in the USA. Estimates were stratified by smoking history and adjusted for education, body mass index and race. uCd was associated with cancer mortality (aHR per twofold higher uCd for men: 1.26 and for women: 1.21). In men, mortality from lung cancer, pancreatic cancer and non-Hodgkin lymphoma was associated with uCd; an association with leukaemia mortality was suggested. In women, associations were suggested with mortality due to lung cancer, leukaemia, ovarian and uterine cancer, but evidence was weaker than in men. It was concluded that cadmium appears to be associated with overall cancer mortality in men and women, but the specific cancers associated differ between men and women, suggesting avenues for future research [219].

Inorganic lead

Evaluation of the carcinogenicity of lead for humans has been based primarily on the results of studies on occupationally exposed men, although gender differences in lead metabolism have been reported. In addition, most of the previous studies have been limited by a failure to identify and control for co-exposures to other known occupational carcinogens. The present study follows an industrial cohort of workers, mostly women, with moderate lead exposure and no confounding by other occupational exposures. Workers, employed at least 2 years between 1950 and 1978 in manual and mechanical (linotype) typesetting and type foundries in 27 printing plants in Moscow, were included in the cohort, which comprised 1423 men and 3102 women. The cohort was followed up during 1979-2003 and contributed 93.682 person-years of observation. Follow-up was 98 percent complete. Standardised mortality ratios (SMRs) and 95 percent confidence interval, based on mortality rates of the Moscow general population and adjusted for gender, age and calendar time, were calculated for the total cohort as well as subcohorts stratified by various exposure parameters. Among women, mortality from all causes, circulatory diseases and all cancers combined was lower than that in the Moscow general population and was similar across work groups. Among men, there was excess overall mortality, mainly due to increased mortality from ischaemic heart disease. For both sexes, no significant excess risk for any cancer site was observed, although some dose-response patterns were found. In the overall cohort, mortality from cancers of the kidney and pancreas increased up to twofold in the highest tertile of cumulative lead exposure based on duration and a relative ranking of the three subcohorts (9 deaths; SMR 2.12, 95 percent confidence interval 1.10 to 4.07) and (18 deaths; SMR 2.32, 95 percent confidence interval 1.46 to 3.68), respectively. Similar mortality trends for these two cancers were found in analyses by gender. It was concluded that consistencies by gender and exposure level make a strong case for a link between exposure to inorganic lead and cancers of the kidney and pancreas [220].

Metal industry

Population exposure to emissions from multiple industrial sources, though little studied, is an aspect of great interest from an epidemiologic standpoint. To investigate whether risk of dying due to tumors of the digestive system in populations residing in the vicinity of Spanish metal production and processing installations increases with proximity to a greater number of industrial facilities. An ecologic study was designed to ascertain municipal mortality due to malignant tumors of the digestive system (oral cavity and pharynx, esophagus, stomach, pancreas, liver, gallbladder and colon-rectum) during the period 1994-2003, in Spanish regions with the presence of multiple industrial sources in the metal sector. Population exposure to pollution was estimated on the basis of distance from town of residence to pollution source. Using Poisson regression models, we analyzed: the increased risk of dying of cancer with proximity to a given number of sources; and excess mortality in the vicinity of specific industrial clusters. The tumor responsible for the greatest number of regions with increased risk in both sexes was liver cancer (78 % of the regions, being statistically

significant in Valencia, Madrid, and the Basque Country) followed by colorectal and pancreatic cancers (56 % of the regions, being statistically significant in Valencia and Zaragoza for colorectal cancer; and Valladolid and Barcelona for pancreatic cancer). Valencia was the province that displayed increased risk with the proximity to metal industries for all tumors studied, while the Basque Country was the Autonomous Region that registered a rising risk trend for liver, stomach and colorectal tumors with proximity (\leq 5 km) to a greater number of sources. The results could support the hypothesis that mortality due to certain tumors of the digestive system increases with proximity (\leq 5 km) to a greater number of metal industry sources. Nevertheless, in this type of ecologic study, conclusions cannot be obtained in terms of cause and effect, nor can individual inferences be made from grouped data [221].

Oral microbiota

The associations between oral diseases and increased risk of pancreatic cancer have been reported in several prospective cohort studies. In one study, it was measured variations of salivary microbiota and evaluated their potential associations with pancreatic cancer and chronic pancreatitis. The study was divided into three phases: (1) microbial profiling using the Human Oral Microbe Identification Microarray to investigate salivary microbiota variation between 10 resectable patients with pancreatic cancer and 10 matched healthy controls, (2) identification and verification of bacterial candidates by real-time quantitative PCR (gPCR) and (3) validation of bacterial candidates by gPCR on an independent cohort of 28 resectable pancreatic cancer, 28 matched healthy control and 27 chronic pancreatitis samples. Comprehensive comparison of the salivary microbiota between patients with pancreatic cancer and healthy control subjects revealed a significant variation of salivary microflora. Thirty-one bacterial species/clusters were increased in the saliva of patients with pancreatic cancer (n=10) in comparison to those of the healthy controls (n=10), whereas 25 bacterial species/clusters were decreased. Two out of six bacterial candidates (Neisseria elongata and Streptococcus mitis) were validated using the independent samples, showing significant variation between patients with pancreatic cancer and controls (n=56). Additionally, two bacteria (Granulicatella adiacens and S mitis) showed significant variation between chronic pancreatitis samples and controls (n=55). The combination of two bacterial biomarkers (N elongata and S mitis) yielded a receiver operating characteristic plot area under the curve value of 0.90 with a 96 percent sensitivity and 82 percent specificity in distinguishing patients with pancreatic cancer from healthy subjects. The authors observed associations between variations of patients' salivary microbiota with pancreatic cancer and chronic pancreatitis. This report also provides proof of salivary microbiota as an informative source for discovering non-invasive biomarkers of systemic diseases [222].

Covariation with other cancer

All types

Several environmental risk factors are known to predispose individuals to pancreatic cancer, and up to 15 percent of pancreatic cancers have an inherited component. Understanding metachronous cancer associations can modify pancreas cancer risk. The objective of this study was to investigate the association of nonpancreatic cancers with subsequent pancreatic adenocarcinoma. The authors used data from the US Surveillance, Epidemiology, and End Results (SEER) registries to identify 1,618,834 individuals who had a primary malignancy and subsequent pancreatic adenocarcinoma (n=4013). Standardized incidence ratios were calculated as an approximation of relative risk (RR) for the occurrence of pancreatic adenocarcinoma after another primary malignancy. Among patients who were diagnosed with a first primary malignancy at ages 20 to 49 years, the risk of subsequent pancreatic adenocarcinoma was increased among patients who had cancers of the ascending colon (relative risk [RR], 4.62; 95 % confidence interval 1.86 to 9.52), hepatic

flexure (RR, 5.42), biliary system (RR, 13.14), breast (RR, 1.32), uterine cervix (RR, 1.61), testes (RR, 2.78), and hematopoietic system (RR, 1.83). Among patients who had a first malignancy at ages 50 to 64 years, the risk was increased after cancers of the stomach (RR, 1.88), hepatic flexure (RR, 2.25), lung and bronchus (RR, 1.46), pharynx (RR, 2.26), and bladder (RR, 1.24). Among patients who had a primary cancer after age 65 years, the risk was increased after cancers of the stomach (RR, 1.79), hepatic flexure (RR, 1.76), biliary system (RR, 2.35), and uterus (RR, 1.23). The results from the current population-based data set suggested that pancreatic adenocarcinoma is associated with certain primary cancers. Genetic predisposition and common environmental and behavioral risk factors all may contribute to this observation. Specific tumor associations will guide future risk-stratification efforts [223].

Prostatic cancer

As the prevalence of prostate cancer is increasing, the issue of subsequent primary cancer (SPC) becomes more relevant. The aim of one study was to estimate the risk and its changes over time of developing SPC among prostate cancer patients compared with the general male population. Utilizing data from the Population-Based Cancer Registry Bavaria, the risk of SPC was evaluated in 59 259 men with prostate cancer diagnosed between 2002 and 2008 who contributed 159 892 person-years. The relative and absolute risk of developing SPC was calculated using the standardized incidence ratio (SIR) and the excess absolute risk. Changes in the risk were examined by plotting the SIR and its 95 percent confidence interval against time after the diagnosis of prostate cancer. The overall risk of SPC was significantly increased by 14% compared with the general male population. With regard to specific cancer types, a significantly increased risk of SPC was found for the urinary bladder, kidney, pancreas, melanoma of skin, leukemia, myeloma, brain/nervous system, renal pelvis/ureter, thyroid, and the small intestine. The absolute risk of SPC for most cancer types, however, was below 10 cases per 10 000 person-years. A significantly decreased risk of SPC was found in the lung/bronchus and the liver. Although detection bias cannot be excluded as a contributing factor for our results, it was recommended continuing follow-up care of prostate cancer patients particularly with respect to SPC of the urinary system as a precaution [224].

Seminoma

To determine the use of adjuvant external beam radiotherapy (EBRT) for patients with clinical stage I testicular seminoma in the USA and to quantify the risk of specific second primary malignancies (SPMs) associated with radiation exposure in these patients it was used the Surveillance, Epidemiology and End Results database to identify patients diagnosed with clinical stage I testicular seminoma between 1973 and 2000. It was evaluated the use of EBRT in these patients and calculated standardized incidence ratios of specific SPMs in these patients. It was stratified the incidence of SPMs based on age at seminoma diagnosis and time to SPM from initial seminoma diagnosis. Adjuvant EBRT use declined from the first decade of the study period to the last decade of the study period (81 % vs 70 %). Overall, there was a 19 percent increase in SPMs in patients exposed to EBRT (observed/expected, O/E, 1.51; 95 % confidence interval 1.08 to 1.31) compared to the general population. Specifically, significantly increased risks were observed for thyroid cancer, pancreatic cancer (O/E, 2.38; 95 % confidence interval 1.43 to 3.72), non-bladder urothelial malignancies, bladder cancer, all haematological malignancies, and non-Hodgkin's lymphoma. Patients had a persistently elevated risk of SPMs 15 years from the time of initial clinical stage I testicular seminoma diagnosis (O/E, 1.29; 95% CI, 1.10-1.49). It was confirmed the increased risk of SPMs after EBRT for seminoma, and it was identified the specific types of SPMs that develop. The risk of EBRT-associated SPM persists for years after the initial seminoma diagnosis, and patients should be informed about these long-term risks [225].

Photon radiotherapy has been the standard adjuvant treatment for stage I seminoma. Singledose carboplatin therapy and observation have emerged as alternative options due to concerns for acute toxicities and secondary malignancies from radiation. In this institutional review board-approved study, it was compared photon and proton radiotherapy for stage I seminoma and the predicted rates of excess secondary malignancies for both treatment modalities. Computed tomography images from 10 consecutive patients with stage I seminoma were used to quantify dosimetric differences between photon and proton therapies. Structures reported to be at increased risk for secondary malignancies and in-field critical structures were contoured. Reported models of organ-specific radiation-induced cancer incidence rates based on organ equivalent dose were used to determine the excess absolute risk of secondary malignancies. Calculated values were compared with tumor registry reports of excess secondary malignancies among testicular cancer survivors. Photon and proton plans provided comparable target volume coverage. Proton plans delivered significantly lower mean doses to all examined normal tissues, except for the kidneys. The greatest absolute reduction in mean dose was observed for the stomach (119 cGy for proton plans vs 768 cGy for photon plans). Significantly more excess secondary cancers per 10,000 patients/year were predicted for photon radiation than for proton radiation to the stomach (4.11; 95 % confidence interval 3.22 to 5.01), large bowel (0.81), and bladder (0.03), while no difference was demonstrated for radiation to the pancreas (0.02). It was concluded that for patients with stage I seminoma, proton radiation therapy reduced the predicted secondary cancer risk compared with photon therapy. It was predicted a reduction of one additional secondary cancer for every 50 patients with a life expectancy of 40 years from the time of radiation treatment with protons instead of photons. Proton radiation therapy also allowed significant sparing of most critical structures examined and warrants further study for patients with seminoma, to decrease radiation-induced toxicity [226].

Extrapancreatic malignancies

To investigate the incidence, characteristics, and prognostic impact of prior extrapancreatic malignancies on patients with pancreatic cancer (PDAC). Records from 1733 patients who underwent surgery for PDAC were analyzed for the occurrence of prior extrapancreatic malignancies. Patients' records showing extrapancreatic malignancies were then analyzed for tumor type, epidemiological data, risk factors, PDAC tumor stage, and long-term survival. A total of 239 patients with PDAC (14 %) had a history of 271 extrapancreatic tumors; 26 patients had a history of two pancreatic cancers, and 3 patients had 3 extrapancreatic cancers. The most common extrapancreatic tumors were breast cancer (56 patients) and prostate cancer (41 patients), followed by colorectal, reno/urothelial, and gynecologic tumors (39, 32, and 23 patients, respectively). No significant difference in overall survival was found between patients with PDAC with or without extrapancreatic malignancies. Pancreatic cancer is associated with extrapancreatic malignancies in a remarkable number of patients. A history of extrapancreatic malignancies does not influence prognosis and should not be an obstacle to a curative therapeutic approach. Surveillance of patients with extrapancreatic malignancies, especially breast, prostate, and colorectal cancer, could allow for earlier PDAC diagnosis and therefore improve prognosis of these patients [227].

Covariation with chronic obstructive pulmonary disease

Little is known about the risk of cancer in patients with chronic obstructive pulmonary disease (COPD), including which cancer sites are most affected. We examined the short- and long-term risk of lung and extrapulmonary cancer in a nationwide cohort of COPD patients. The study was linked to the Danish National Registry of Patients and the nationwide cancer registry, and examined the incidence of various cancers in 236,494 individuals with a first incident hospital contact with COPD during 1980-2008. The observed cancer incidence in this cohort was compared with the expected incidence in the general population on the basis of national age-, sex-, and site-specific incidence rates. Median follow-up was 3.5 years. During the first year of follow-up, 9434 cancers were diagnosed in COPD patients

(standardized incidence ratio, SIR, 3.1; 95 % confidence interval 3.0 to 3.2). The 1-year SIR was 8.5 for lung cancer, for all tobacco-related cancers, and 1.9 for other cancers. In the following years, cancer incidence was increased 1.4-fold in COPD patients. These patients had an increased risk of developing tobacco-related cancers (SIR 2.1), including cancers of the lung, larynx, tongue, oral cavity, pharynx, esophagus, stomach, liver, pancreas, cervix uteri, and urinary tract (with SIRs ranging between 1.3 and 2.8). It was concluded that patients with first-time hospital-diagnosed COPD are at considerably increased risk of developing both lung cancer and extrapulmonary cancers. Physicians should be aware of cancer in COPD patients [228].

Hypertension

Observational studies have shown inconsistent results for the association between blood pressure and cancer risk. It was investigated the association in 7 cohorts from Norway, Austria, and Sweden. In total, 577799 adults with a mean age of 44 years were followed for, on average, 12 years. Incident cancers were 22184 in men and 14744 in women, and cancer deaths were 8724 and 4525, respectively. Cox regression was used to calculate hazard ratios of cancer per 10 mmHg increments of midblood pressure, which corresponded with 0.7 SDs and, for example, an increment of systolic/diastolic blood pressure of 130/80 to 142/88 mmHg. All of the models used age as the time scale and were adjusted for possible confounders, including body mass index and smoking status. In men, midblood pressure was positively related to total incident cancer (hazard ratio per 10 mmHg increment: 1.07; 95 % confidence interval 1.04 to 1.09]) and to cancer of the oropharynx, colon, rectum, lung, bladder, kidney, malignant melanoma, and nonmelanoma skin cancer. In women, midblood pressure was not related to total incident cancer but was positively related to cancer of the liver, pancreas, cervix, uterine corpus, and malignant melanoma. A positive association was also found for cancer mortality, with HRs per 10 mmHg increment of 1.12 for men and 1.06 for women. These results suggest a small increased cancer risk overall in men with elevated blood pressure level and a higher risk for cancer death in men and women [229].

Helicobacter

Recognition of Helicobacter pylori as an important factor in genesis of gastric adenocarcinoma lead to a large number of studies concerning potential role of Helicobacter spp. in the development of extragastric digestive malignancies. The serological studies indicated possible localizations in the digestive system being from interest in enlightening Helicobacter spp. carcinogenic potential. The PCR obtruded itself as a gold standard in proving existence of actual correlation. In this review, the authors have examined studies conducted in the last 10 years examining Helicobacter spp. correlation with extragastric digestive carcinogenesis. Studies have been observed in four groups referring to hepatic carcinoma, bile duct cancer, pancreatic cancer, and colon cancer. The results of these researches have shown that there is a strong correlation between Helicobacter spp. colonization and primary liver tumors as well as bile duct tumors, whereas conclusions made by authors examining pancreatic cancer are contradictory and demands further investigation. No correlation between Helicobacter spp. and colon cancer have been proven. The PCR subtype most widely used in studies included in this review was nested PCR, whereas genes targeted most frequently for amplification are 16S rDNA of Helicobacter spp. and UreA gene or caqA gene of H. pylori. During the last 10 years PCR has proven itself as a sovereign method for Helicobacter spp. diagnostic in extragastric organs in the digestive system. Knowledge and experiences obtained in this domain could be encouraging for researchers in analogous fields of interest [230].

Molecular biology

Molecular markers in general

The purpose of this study was to investigate the clinical feasibility and utility of low-density array analysis on samples obtained from endoscopic ultrasound-guided fine needle aspiration biopsy in locally advanced and/or metastatic pancreatic ductal adenocarcinoma and chronic pancreatitis. In this prospective multicenter study, it was quantified candidate gene expression in biopsies sampled from 44 locally advanced and/or metastatic pancreatic carcinoma and from 17 pseudotumoural chronic pancreatitis using dedicated low-density array microfluidic plates. It was first demonstrated that 18S gene expression is stable and comparable in normal pancreas and pancreatic cancer tissues. Next, it was found that eight genes (S100P, PLAT, PLAU, MSLN, MMP-11, MMP-7, KRT7, KRT17) were significantly over expressed in pancreatic cancer samples when compared to pseudotumoural chronic pancreatitis. Linear discriminative analysis identified S100P, PLAT, MSLN, MMP-7, KRT7 as highly explicative variables. The area under receiver operating curve establishes the clinical validity of the potential diagnostic markers identified in this study. In addition, combination of S100P and KRT7 gave better diagnosis performances (Area Under Receiver Operating Curve 0.81, sensitivity 81 %, specificity 77 %). It was thus demonstrated that molecular studies on EUS-guided FNA material are feasible for the identification and guantification of markers in PDAC patients diagnosed with non-resectable tumours. Using low-density array, it was isolated a molecular signature of advanced pancreatic carcinoma including mostly cancer invasion-related genes. This work stems for the use of novel biomarkers for the molecular diagnosis of patient with solid pancreatic masses [231].

Proteomics

Pancreatic ductal adenocarcinoma (PDAC) is a major cause of cancer-related death, largely due to metastatic disease. To better understand PDAC metastatic spread and identify novel therapeutic targets, we analysed the proteome of primary tumours and matched lymph node (LN) metastases. As frozen specimens of metastatic lesions are scarce, we examined formalin-fixed paraffin-embedded (FFPE) tissues. This poses technical challenges because of the cross-linkages induced by fixation. Using laser capture microdissection (PALM system), we isolated malignant epithelia from seven FFPE primary PDAC tumours and matched LN metastases. Following dissection, samples were analysed in duplicate using Multidimensional Protein Identification Technology (MudPIT); this resulted in the identification of 1504 proteins, 854 of which were common to all samples analysed. Comparison of the obtained proteins with data from previous proteomics studies on pancreatic tissue, pancreatic juice, serum, and urine resulted in a less than 30 percent overlap, indicating that our study has substantially expanded the current database of proteins expressed in this malignancy. Statistical analysis further showed that 115/854 proteins (14 %) were significantly differentially expressed (g-value \geq 3.8). Two proteins, S100P and 14-3-3 sigma, with highly significant g-values were confirmed to be significantly differentially expressed in a larger series of 55 cases of matched primary PDAC and LN metastases using immunohistochemistry. Thus, laser capture microdissection of FFPE tissue coupled with downstream proteomic analysis is a valid approach for the investigation of metastatic PDAC. This is the first study to establish and compare the protein composition of primary PDAC and matched LN metastases, and has resulted in the identification of several potential epithelialspecific therapeutic targets, including 14-3-3 sigma and S100P [232].

Proteoms of pancreatic juice

The aims of one study were to characterize the proteome of normal pancreatic juice, to analyze the effect of secretin on the normal proteome, and to compare these results with published data from patients with pancreatic cancer. Paired pancreatic fluid specimens (before and after intravenous secretin stimulation) were obtained during endoscopic pancreatography from 3 patients without significant pancreatic pathology. Proteins were identified and quantified by mass spectrometry-based protein quantification technology. The human RefSeq (NCBI) database was used to compare the data in samples from patients without pancreatic disease with published data from 3 patients with pancreatic cancer. A total of 285 proteins were identified in normal pancreatic juice. Ninety had sufficient amino acid sequences identified to characterize the protein with a high level of confidence. All 90 proteins were present before and after secretin administration but with altered relative concentrations, usually by 1 to 2 folds, after stimulation. Comparison with 170 published pancreatic cancer proteins multiple proteins related to many biological processes. Secretin alters the concentration but not the spectrum of these proteins. The pancreatic juice proteome of patients without pancreatic disease and that of patients with pancreatic cancer differ markedly [233].

Adiponectin

Excess body weight and type 2 diabetes mellitus, risk factors of pancreatic cancer, are characterized by decreased levels of adiponectin. In addition to anti-inflammatory and antiproliferative actions, adiponectin has an important role in regulating glucose metabolism, i.e. decreasing circulating blood glucose levels. Prospectively, hyperglycemia has been associated with risk of pancreatic cancer. The aim of one study was to investigate the association of pre-diagnostic adiponectin levels with pancreatic cancer risk. It was conducted a case-control study nested within European Prospective Investigation into Cancer and Nutrition. Blood samples of 452 pancreatic cancer cases and 452 individually matched controls were analyzed by immunoassays. Multivariate conditional logistic regression was used to estimate odds ratios (OR). Overall, adiponectin showed no association with pancreas cancer risk; however, among never smokers, higher circulating levels of adiponectin were associated with a reduction in pancreatic cancer risk (OR 0.44 for highest vs lowest guartile). whereas among current smokers there was no significant association (OR 1.59 for highest vs lowest quartile). In the study, lower adiponectin concentrations may be associated with the development of pancreatic cancer among never smokers, whereas the only other prospective study being conducted so far showed a decrease in risk among male smokers. Therefore, further studies are needed to clarify the role of adjoonectin in pancreatic cancer development [234].

Angiogenesis

Anti-angiogenic agents are now being clinically evaluated for the treatment of pancreatic cancer and a detailed investigation of the angiogenic profile of pancreatic cancer is needed. The aim of this study was to evaluate the plasma concentrations of angiogenesis-related molecules in patients with pancreatic cancer, compared with those with other diseases. Plasma samples obtained from 45 patients with pancreatic cancer were analyzed and compared with those from 9 patients with pancreatitis, 16 patients with benign hepatobiliary diseases and 58 patients with colorectal cancers. The plasma levels of angiogenesis-related molecules including angiopoietin-2, follistatin, granulocyte-colony stimulating factor, hepatocyte growth factor, interleukin-8, leptin, platelet-derived growth factor beta polypeptide, platelet endothelial cell adhesion molecule-1 and vascular endothelial growth factor were determined using an antibody suspension bead arrays system. The plasma levels of all the angiogenesis-related molecules were not increased in patients with pancreatic cancer, compared with those with pancreatitis and benign hepatobiliary diseases, whereas the levels of those with colorectal cancer were markedly increased. The plasma interleukin-8 concentration was significantly elevated in patients with distant metastases and was associated with a poor treatment outcome of chemotherapy in patients with pancreatic

cancer. The plasma levels of angiogenesis-related molecules were not elevated in patients with pancreatic cancer, compared with those with benign diseases or colorectal cancer. The plasma interleukin-8 level may be a novel biomarker for the response to chemotherapy in patients with pancreatic cancer and warrants further prospective study [235].

Cell adhesion molecules

The aim of one study was to develop an immunomagnetic/real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay and assess its clinical value for the molecular detection of circulating tumor cells (CTCs) in peripheral blood of pancreatic cancer patients. The presence of CTCs was evaluated in 34 pancreatic cancer patients before systemic therapy and in 40 healthy controls, through immunomagnetic enrichment, using the antibodies BM7 and VU1D9 (targeting mucin 1 and epithelial cell adhesion molecule, EpCAM), respectively], followed by real-time RT-PCR analysis of the genes KRT19, MUC1, EPCAM, CEACAM5 and BIRC5. The developed assay showed high specificity, as none of the healthy controls were found to be positive for the multimarker gene panel. CTCs were detected in 47.1% of the pancreatic cancer patients before the beginning of systemic treatment. Shorter median progression-free survival (PFS) was observed for patients who had at least one detectable tumor-associated transcript, compared with patients who were CTC negative. Median PFS time was 66 days for patients with baseline CTC positivity and 138 days. The results suggest that in addition to the current prognostic methods, CTC analysis represents a potential complementary tool for prediction of outcome in pancreatic cancer patients [236].

C-terminal tensin-like gene (CTEN)

C-terminal tensin-like gene (CTEN, also known as TNS4) localizes to focal adhesions and is reported to function as an oncogene in colonic, breast, lung, and gastric cancers. Its role in pancreatic cancer is unknown and was thus investigated in this study. C-terminal tensinlike gene expression was evaluated by immunohistochemistry in a series of pancreatic cancers. Functional activity of the CTEN was tested by manipulating cellular CTEN levels using a dual approach of gene knockdown/forced expression. The CTEN is overexpressed in 31 (70 %) of 44 pancreatic cancers. Functionally, changes in CTEN level did not alter cellular proliferation, but CTEN levels were positively associated with enhanced colony-forming efficiency in both Panc-1 and PSN-1 cell lines. Forced CTEN expression in Panc-1 cells stimulated cell motility, whereas knockdown of CTEN in PSN-1 inhibited cell motility in both transwell migration and wound-healing assays. Evaluation of downstream targets demonstrated that alterations in CTEN levels induced changes in focal adhesion kinase and E-cadherin, whereas integrin-linked kinase (ILK) remained unchanged. These are the first data showing an oncogenic role for CTEN in pancreatic cancer through promotion of colony formation and cell motility. The latter may be mediated by signaling through focal adhesion kinase and inhibiting E-cadherin [237].

EGFR

Pancreatic and periampullary cancers have a high incidence of activating KRAS mutations. The aim of one study was to determine the incidence of KRAS and EGFR mutations in pancreatic and periampullary cancers and their relationship with survival. One hundred patients undergoing pancreaticoduodenectomy or pancreatic biopsy for cancer were recruited. Samples of formalin-fixed paraffin-embedded or fresh pancreatic tissue were obtained. EGFR was analyzed by DNA sequencing of exons 18 to 21. KRAS was analyzed by pyrosequencing of codons 12, 13, and 61. EGFR mutations were found in 2 (2 %) of 88 assessable cases. One in exon 18 (c.1966C>T, p.Q710X) and 1 in exon 19 (c.2066A>G, p.E734G). A synonymous single-nucleotide polymorphism in exon 20 (c.2361G>A, p.Q787)

was identified in 57 (68 %) of 84 patients studied. Twenty-eight (41 %) of 68 cases harbored a point mutation in KRAS codon 12 (26 cases) and codon 61 (2 cases). The overall median survival was 308 days (range, 7-2623 days). The presence of KRAS point mutations did not significantly alter median survival time (23 vs 28 months). EGFR somatic mutations are rare in pancreatobiliary malignancies. KRAS mutations are less common than previous reports and do not correlate with survival [238].

Fibers

Scanty and inconsistent studies are available on the relation between dietary fiber intake and pancreatic cancer. A case-control study was carried out in to further investigate the role of various types of dietary fibers in the etiology of pancreatic cancer. Cases were 326 patients with incident pancreatic cancer, excluding neuroendocrine tumors, admitted to major teaching and general hospitals during 1991-2008. Controls were 652 patients admitted for acute, nonneoplastic conditions to the same hospital network of cases. Information was elicited using a validated food frequency questionnaire. Odds ratios (ORs) and the corresponding 95 percent confidence intervals were estimated for intake quintiles of different types of fiber after allowance for total energy intake and other potential confounding factors. Total fiber intake was inversely related to risk of pancreatic cancer (OR 0.4 for highest versus lowest quintile of intake). An inverse association emerged between pancreatic cancer and both soluble (OR 0.4) and total insoluble fiber (OR 0.5), particularly cellulose (OR 0.4) and lignin (OR 0.5). Fruit fiber intake was inversely associated with pancreatic cancer (OR 0.5), whereas grain fiber was not (OR 1.2). This study suggests that selected types of fiber and total fiber are inversely related to pancreatic cancer [239].

HSP70

Heat shock protein 70 (HSP70) is overexpressed in human pancreatic cancer cell lines. To determine if serum HSP70 levels are elevated in patients with pancreatic cancer and can function as a biomarker for early detection of pancreatic cancer study subjects were divided into 3 groups: histologically proven pancreatic cancer (PC; n=23), chronic pancreatitis (CP; n=12), and matched normal control subjects (C; n=10). Serum HSP70 levels were determined using a novel immunoelectrophoresis method developed and validated by the authors. Significance of difference between the groups was analyzed with analysis of variance (ANOVA). Receiver operating characteristic (ROC) curve analysis was performed to discriminate patients with pancreatic cancer from normal controls. The mean \pm SE serum HSP70 levels in the PC, CP, and C groups were 1.68 \pm 0.083 ng/mL, 0.40 \pm 0.057 ng/mL, and 0.04 ng/mL, respectively. Serum HSP70 levels in the PC group were significantly higher compared with either the CP or C groups. The sensitivity and specificity of elevated serum HSP70 levels are significantly increased in patients with pancreatic cancer and may be useful as an additional biomarker for the detection of pancreatic cancer [240].

Hyperfucosylated lactosamines

The prognosis for a patient with pancreatic cancer is considerably improved when the malignant lesions are identified at an early stage of the disease and removed by surgical resection. Unfortunately, the absence of a practical screening strategy and clinical diagnostic test for identifying pre-malignant lesions within the pancreas often prevents early detection of pancreatic cancer. To aid in the development of a molecular screening system for early detection of the disease, it was performed glycomic and glycoproteomic profiling experiments on 21 pancreatic cyst fluid samples, including fluids from mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN), two types of mucinous cysts, which are considered high-risk to undergo malignant transformation. A total of 80 asparagine-linked

(N-linked) glycans, including high-mannose and complex structures, were identified. Of special interest was a series of complex N-linked glycans containing two to six fucose residues, located predominantly as substituents on β -lactosamine extensions. Following the observation of these hyperfucosylated glycans, bottom-up proteomics experiments utilizing a label-free quantitative approach were applied to the investigation of two sets of tryptically-digested proteins derived from the cyst fluids: all soluble proteins in the raw samples and a subproteome of the soluble cyst fluid proteins that were selectively enriched for fucosylation through the use of surface-immobilized Aleuria aurantia lectin (AAL). A comparative analysis of these two proteomic data sets identified glycoproteins that were significantly enriched by lectin affinity. Several candidate glycoproteins that appear hyperfucosylated were identified, including triacylglycerol lipase and pancreatic alpha-amylase, which were 20- and 22-fold more abundant, respectively, following AAL enrichment [241].

IGF-1

Early diagnosis of pancreatic cancer (PC) in diabetic patients is difficult owing to late presentation of symptoms. Hence, finding a marker to identify cancer stage early would be useful to improve survival. It was aimed to determine levels of serum retinol binding protein 4 (RBP-4), neutrophil gelatinase-associated lipocalin (NGAL), insulin-like growth factor I (IGF-I), and its binding protein 3 (IGFBP-3) in patients with PC with preexisting type 2 diabetes. Moreover, we assessed their clinical usefulness in PC diagnosis and their association with tumor severity. Twenty-three patients with PC, 32 diabetic patients, and 20 healthy controls were examined. Preoperative and postoperative samples were obtained from 15 patients with PC. Serum insulin, cancer antigen (CA 19-9), RBP-4, NGAL, IGF-I, and IGFBP-3 levels were estimated by enzyme-linked immunosorbent assay. Significant elevation in the levels of RBP-4, NGAL, and IGF-I together with significant reduction in the level of IGFBP-3 was found in patients with pancreatic cancer. Moreover, RBP-4 and NGAL levels were reduced in postoperative samples compared with preoperative ones. Receiver operating characteristic curve analysis revealed that they can distinguish PC from non-PC cases with significant area under the curve. Retinol binding protein 4, NGAL, IGF-I, and IGFBP-3 are associated with PC in type 2 diabetic patients. They could be useful in distinguishing PC from non-PC cases when used in combination or with cancer antigen [242].

Lymphangiogenesis

Lymphatic vessels in primary tumor tissue play an important role in lymphatic metastasis. Lymphatic metastasis of malignant neoplasms is significantly related to prognosis, influencing both recurrence and survival. The aim of this study was to investigate the correlation of intra-tumoral lymphatic vessel density (iLVD) and peri-tumoral lymphatic vessel density (pLVD) with biological behavior and prognostic parameters in pancreatic carcinoma (PC) and other pancreatic tumors. Lymphangiogenesis was examined using the D2-40 monoclonal antibody in 33 cases of PC, 7 neuroendocrine tumors of the pancreas (NETP), 7 solid pseudopapillary tumors of the pancreas (SPTP) and 3 cystadenomas of the pancreas (CP). Positively-stained microvessels were counted at magnification x400 in dense lymphatic vascular foci (hotspots). The LVD of PC was compared to 3 other pancreatic tumors. The relationships among the LVD, the extent of differentiation, lymphatic invasion, lymph node metastasis and other clinicopathological parameters of PC were analyzed. There was no difference in the iLVD among PC, NETP, SPTP and CP. The pLVD of NETP was markedly higher than that of PC, SPTP and CP. The pLVD of PC was significantly higher than that of SPTP and CP, but there was no difference between SPTP and CP. The pLVD of PC was significantly associated with the extent of differentiation, lymphatic invasion and lymph node metastasis, whereas it was not associated with age, gender, tumor size, tumor location and peri-pancreatic invasion. The iLVD of PC was not correlated with these clinicopathological parameters. There was no difference in iLVD and no marked difference in pLVD among the

pancreatic tumors. Detection of pLVD is of greater importance than detecting iLVD in these pancreatic tumors, as pLVD can be utilized for the prediction of lymph node metastasis, thus aiding in the evaluation of patient prognosis [243].

miRNAs

One study aimed to evaluate microRNA (miRNA) expression in pancreatic resection specimens and fine needle aspiration biopsies and determine which, if any, miRNAs aid the distinction between benign and malignant pancreatic tumors in limited cytology material. Resection specimens containing adenocarcinoma (n=17), intraductal papillary mucinous neoplasms (n=11), and nonneoplastic tissues (n=15) were evaluated for miR-21, miR-221, miR-100, miR-155, and miR-181b expression by quantitative reverse transcriptase polymerase chain reaction (gRT-PCR), and a subset of carcinomas and intraductal papillary mucinous neoplasms was analyzed with miRNA microarrays. Cellblocks containing carcinoma (n=26) or benign pancreatic lesions (n=11) from fine needle aspiration biopsies were subjected to gRT-PCR for miR-21, miR-221, miR-181b, miR-196a, and miR-217. Carcinomas showed higher expression of miR-21, miR-221, miR-155, miR-100, and miR-181b than benign lesions by qRT-PCR, and overexpression of miR-21, miR-221, and miR-181b was confirmed by microarray analysis. Cellblocks containing carcinoma showed higher expression of miR-21, miR-221, and miR-196a than those from benign lesions. In conclusion pancreatic ductal adenocarcinomas show differential expression of miRNAs compared to benign pancreatic lesions. A select panel of miRNAs aids the distinction between pancreatic lesions in cytology specimens [244].

Extensive studies have been performed in order to identify biomarkers for the disease. Some have been or are currently being evaluated, such as CEACAM-1, MIC-1, PAM4 and CA19-9; the last is the only blood-borne biomarker in routine clinical use for management of pancreatic cancer. At the level of messenger RNA (mRNA), quite a few, including some very specific molecular variations have been found in tissue. However, none of these markers has proven helpful in facilitating diagnosis, largely due to the real difficulty in obtaining biopsy material and the dilemma that the performance of biopsies is inappropriate without prior indication of disease. More recently, microRNAs (miRNAs) have gained attention as possible biomarkers. They belong to the group of small non-coding RNAs and have essential functions in various biological processes. In addition, the molecules are stable in comparison to mRNA, which is of considerable importance for the robustness of diagnostic assays. About 1000 miRNAs are believed to occur in humans and are considered to form a distinct layer of regulation of cellular function. Several miRNAs were found to be associated with tumorrelevant processes. Similar to mRNA profiling, miRNA signatures exhibited distinctive expression variations in pancreatic tumor samples, chronic pancreatitis tissue and normal pancreas. Expression abnormalities in pancreatic endocrine and acinar tumors were associated with distinctive pathologic features and clinical behavior. Also, a relationship of the expression of particular miRNA and survival of patients with pancreatic adenocarcinoma was reported. The transcripts miR-21, miR-155, miR-203, miR-210 and miR-222 were described as potential predictors of survival. However, the tissue-based miRNA studies also suffer from the fact that invasive action is required to acquire material for analysis, and as such, tissue-based miRNA profiling does not offer significant progress compared to messenger RNA profiling but for the superior stability of miRNA. Markers that occur in peripheral blood or other body fluids would be best for detection. For various tumor entities, extracellular nucleic acids have been found in serum, for example. In part, they have their origin in circulating tumor cells. Moreover, the actual tumor cells themselves could be isolated from blood and used as a means for diagnosis and prognosis. Accumulating data have become available which indicate that a diagnosis of different forms of disease, including cancers, may be possible by analyzing the miRNA levels in serum. For pancreatic cancer, an analysis of the variations in plasma of four miRNAs has been reported. The measurement of miRNAs in blood offers an option for the non-invasive detection of chronic pancreatitis or

pancreatic cancer. The miRNA assay combines a minimally invasive nature with a robustness of the analyte molecules. The miRNA signatures exhibited enough reproducibility between patients for a robust detection of disease. The number of marker molecules required for such a result is nevertheless small enough to fit to assay systems used in routine diagnostics, in particular real-time PCR. Now both blood and tissue samples were taken from patients with pancreatic ductal adenocarcinoma, chronic pancreatitis or from healthy individuals. From the results, highly accurate molecular classifiers could be defined. In addition, the variations observed in blood and tissue were compared in order to detect possible functional connections between them. The blood analysis permitted distinction of healthy and diseased pancreas but did not yield sufficient information to separate pancreatic inflammation from cancer. The tissue analysis, however, showed differences between inflammation and tumor. In combination, this process may enable a differential and initially minimally invasive identification of disease, in particular for the evaluation of tumor reoccurrence in patients, who have undergone curative surgical resection, and for people with a familial risk of pancreatic cancer. Variations in the abundance of all microRNA molecules from peripheral blood cells and pancreas tissues were analyzed on microarrays and in part validated by real-time PCR assays. In total, 245 samples from two clinical centers were studied that were obtained from patients with pancreatic ductal adenocarcinoma or chronic pancreatitis and from healthy donors. Utilizing the minimally invasive blood test, receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) analysis demonstrated very high sensitivity and specificity of a distinction between healthy people and patients with either cancer or chronic pancreatitis; respective AUC values of 0.973 and 0.950 were obtained. Confirmative and partly even more discriminative diagnosis could be performed on tissue samples with AUC values of 1.0 and 0.937. respectively. In addition, discrimination between cancer and chronic pancreatitis was achieved. Also, several miRNAs were identified that exhibited abundance variations in both tissue and blood samples. The results could have an immediate diagnostic value for the evaluation of tumor reoccurrence in patients, who have undergone curative surgical resection, and for people with a familial risk of pancreatic cancer. The hypothesis exists that inflammation, such as chronic pancreatitis, could be required as one step toward the development of pancreatic cancer. Given the fact that not all cases of pancreatic cancer are associated with chronic pancreatitis, it could be that other forms of inflammation have a similar effect. Although the actual inflammation may have occurred earlier and even gone unnoticed phenotypically, it may be possible that a miRNA signature, which is similar to the one observed for chronic pancreatitis, could serve as an indicator for an increased risk of developing pancreatic cancer, while the profiles of other inflammation diseases, such as the ones of chronic sarcoidosis, periodontitis and chronic obstructive pulmonary disease, which are clearly different, do not implicate a risk [245].

M2-polarized tumor-associated macrophages

Tumor-associated macrophages (TAMs) are reportedly involved in lymphangiogenesis in primary tumors, playing a crucial role in lymphatic metastasis. Furthermore, nodal lymphangiogenesis precedes and promotes regional lymph node (RLN) metastasis. It was investigated the relationship of M2-polarized TAM infiltration of the RLNs, nodal lymphangiogenesis, and occult nodal involvement in pN0 pancreatic cancer. Hematoxylineosin-stained primary tumor and regional LN specimens from 40 patients diagnosed with pN0 pancreatic cancer according to the pathological TNM classification were assessed. To evaluate lymphangiogenesis, lymphatic vessel density was measured by using D2-40 antibody. CD163 and cytokeratin AE1/AE3 antibodies were used to detect M2-polarized TAMs and isolated tumor cells in the RLNs, respectively.The nodal lymphatic vessel density had a strong association with the M2-polarized TAM density in the RLNs. Most of these TAMs expressed vascular endothelial growth factor C. Furthermore, in the RLNs, the M2-polarized TAM density was significantly associated with the incidence of isolated tumor cells. Thus, M2-polarized TAM infiltration of RLNs is significantly associated with nodal

lymphangiogenesis and occult nodal involvement in pN0 pancreatic cancer. Node-infiltrating M2-polarized TAMs may facilitate nodal lymphangiogenesis via the production of vascular endothelial growth factor C and thus promote RLN metastasis [246]

mRNA

Extensive studies have been performed in order to identify biomarkers for the disease. Some have been or are currently being evaluated, such as CEACAM-1, MIC-1, PAM4 and CA19-9; the last is the only blood-borne biomarker in routine clinical use for management of pancreatic cancer. At the level of messenger RNA (mRNA), guite a few, including some very specific molecular variations have been found in tissues. However, none of these markers has proven helpful in facilitating diagnosis, largely due to the real difficulty in obtaining biopsy material and the dilemma that the performance of biopsies is inappropriate without prior indication of disease. More recently, microRNAs (miRNAs) have gained attention as possible biomarkers. They belong to the group of small non-coding RNAs and have essential functions in various biological processes. In addition, the molecules are stable in comparison to mRNA, which is of considerable importance for the robustness of diagnostic assays. About 1000 miRNAs are believed to occur in humans and are considered to form a distinct layer of regulation of cellular function. Several miRNAs were found to be associated with tumorrelevant processes. Similar to mRNA profiling, miRNA signatures exhibited distinctive expression variations in pancreatic tumor samples, chronic pancreatitis tissue and normal pancreas. Expression abnormalities in pancreatic endocrine and acinar tumors were associated with distinctive pathologic features and clinical behavior. Also, a relationship of the expression of particular miRNA and survival of patients with pancreatic adenocarcinoma was reported. The transcripts miR-21, miR-155, miR-203, miR-210 and miR-222 were described as potential predictors of survival. However, the tissue-based miRNA studies also suffer from the fact that invasive action is required to acquire material for analysis, and as such, tissue-based miRNA profiling does not offer significant progress compared to messenger RNA profiling but for the superior stability of miRNA. Accumulating data have become available which indicate that a diagnosis of different forms of disease, including cancers, may be possible by analyzing the miRNA levels in serum. For pancreatic cancer, an analysis of the variations in plasma of four miRNAs has been reported. Variations in the abundance of all microRNA molecules from peripheral blood cells and pancreas tissues were analyzed on microarrays and in part validated by real-time PCR assays. In total, 245 samples from two clinical centers were studied that were obtained from patients with pancreatic ductal adenocarcinoma or chronic pancreatitis and from healthy donors. Utilizing the minimally invasive blood test, receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) analysis demonstrated very high sensitivity and specificity of a distinction between healthy people and patients with either cancer or chronic pancreatitis; respective AUC values of 0.973 and 0.950 were obtained. Confirmative and partly even more discriminative diagnosis could be performed on tissue samples with AUC values of 1.0 and 0.937, respectively. In addition, discrimination between cancer and chronic pancreatitis was achieved (AUC 0.875). Also, several miRNAs were identified that exhibited abundance variations in both tissue and blood samples. The measurement of miRNAs in blood offers an option for the non-invasive detection of chronic pancreatitis or pancreatic cancer. The accuracy of discrimination from any other disease is at least 81 percent, even if there is no prior knowledge about the disease status. Even without a therapeutic advance, this result is likely to have clinical consequences by increasing the number of curative resections. Also, for the evaluation of tumor reoccurrence in patients, who have undergone curative surgical resection, and for people with a familial risk of pancreatic cancer, the miRNA analysis could have a substantial effect on survival. The miRNA assay combines a minimally invasive nature with a robustness of the analyte molecules. The miRNA signatures exhibited enough reproducibility between patients for a robust detection of disease. The number of marker molecules required for such a result is nevertheless small enough to fit to assay systems used in routine diagnostics, in particular real-time PCR. Both the blood and the tissue profiling could be supplemented by other data, such as messenger RNA profiles

on tissue biopsy samples or the resected tumor, produced from the very RNA-preparations utilized for miRNA detection. Also the testing of other body fluids and the combination with other analyte forms should improve the solidity and accuracy of non-invasive testing even further. For example, particular protein signatures in urine were recently reported that were indicative for pancreatic ductal carcinoma. The hypothesis exists that inflammation, such as chronic pancreatitis, could be required as one step toward the development of pancreatic cancer. Given the fact that not all cases of pancreatic cancer are associated with chronic pancreatitis, it could be that other forms of inflammation have a similar effect. Although the actual inflammation may have occurred earlier and even gone unnoticed phenotypically, it may be possible that a miRNA signature, which is similar to the one observed for chronic pancreatitis, could serve as an indicator for an increased risk of developing pancreatic cancer, while the profiles of other inflammation diseases, such as the ones of chronic sarcoidosis, periodontitis and chronic obstructive pulmonary disease, which are clearly different, do not implicate a risk [247].

mtDNA

Although the mitochondrial genome exhibits high mutation rates, common mitochondrial DNA (mtDNA) variation has not been consistently associated with pancreatic cancer. Here, it was comprehensively examined mitochondrial genomic variation by sequencing the mtDNA of participants (cases 286, controls 283) in a pancreatic cancer case-control study. Five common variants were associated with pancreatic cancer at nominal statistical significance with the strongest finding for mt5460g in the ND2 gene (OR 3.9) which encodes an A331T substitution. Haplogroup K was nominally associated with reduced pancreatic cancer risk (OR 0.32) when compared with the most common haplogroup, H. A total of 19 haplogroupspecific rare variants yielded nominal statistically significant associations with pancreatic cancer risk, with the majority observed in genes involved in oxidative phosphorylation. Weighted-sum statistics were used to identify an aggregate effect of variants in the 22 mitochondrial tRNAs on pancreatic cancer risk. While the burden of singleton variants in the HV2 and 12S RNA regions was three times higher among European haplogroup N cases than controls, the prevalence of singleton variants in ND4 and ND5 was two to three times higher among African haplogroup L cases than in controls. Together, the results of this study provide evidence that aggregated common and rare variants and the accumulation of singleton variants are important contributors to pancreatic cancer risk [248].

Mucines

Pancreatic cancer is characterized by aggressive growth and resistance to treatment. Identification of unique biomarkers for diagnosis and prognosis is important for treatment of this disease. We investigated the expression patterns of mucin 1 (MUC1), mucin 2 (MUC2) and cytokeratin 17 (CK17) in both normal tissues and metastatic adenocarcinomas using immunohistochemistry (IHC). It has been shown that MUC1 (pan-epithelial membrane mucin), MUC2 (intestinal-type secretory mucin) and CK17 can be used as a panel of markers to distinguish collectively pancreatobiliary carcinoma from other primary site carcinomas. Tumors originating in the pancreatobiliary system showed an expression pattern of MUC1 (+), MUC2 (-) and CK17 (+). By contrast, tumors arising from the colorectal region were MUC1 (-), MUC2 (+) and CK17 (-), while tumors originating from non-pancreatobiliary system tissue expressed a MUC1 (+), MUC2 (-) and CK17 (-) profile. More importantly, the MUC1 (+), MUC2 (-) and CK17 (+) result showed greater sensitivity than CA19-9 by IHC, which is the currently accepted and widely used pancreatic tumor marker for diagnosing pancreatic cancer. Thirteen of 51 cases (25 %) of pancreatobiliary adenocarcinomas with the pattern MUC1 (+), MUC2 (-) and CK17 (+) showed no immunoreactivity for CA19-9, while 34/51 (67 %) cases having MUC1 (+), MUC2 (-) and CK17 (+) were correlated with positive CA19-9 staining. Our data support using an antibody panel of MUC1, MUC2 and CK17 to enhance

current methods for pancreatic cancer diagnosis by identifying specifically the primary tissue of origin [249].

Mucin 16

Mucin 16 (cancer antigen 125) is a cell surface glycoprotein that plays a role in promoting cancer cell growth in ovarian cancer. The aims of one study were to examine mucin 16 expression in a large number of digestive tract adenocarcinomas and precursors and to determine whether mucin 16 up-regulation is correlated with patient outcome. Tissue microarrays were constructed using surgical resection tissues and included pancreatic (115 normal, 29 precursors, 200 pancreatic ductal adenocarcinomas), esophageal (86 normal, 104 precursors, 95 esophageal adenocarcinomas, 35 lymph node metastases), gastric (211 normal, 8 precursors, 119 gastric adenocarcinomas, 62 lymph node metastases), and colorectal (34 normal, 17 precursors, 39 colorectal adenocarcinomas) tissues. Mucin 16 was detected in 82, 70, 41, and 64 percent of the pancreatic ductal adenocarcinomas, esophageal adenocarcinomas, gastric adenocarcinomas, and colorectal adenocarcinomas, respectively. Mucin 16 was seen in a subset of the precursors. On multivariate analysis, moderate/diffuse mucin 16 in pancreatic ductal adenocarcinomas was strongly associated with poor survival, independent of other prognosis predictors. A similar trend was observed for esophageal adenocarcinomas and gastric adenocarcinomas. Focal mucin 16 in colorectal adenocarcinomas was significantly correlated with a better patient outcome, when compared with mucin 16-negative cases. Using Western blot analysis, it was found mucin 16 expression in 3 of 6 pancreatic ductal adenocarcinoma and 1 of 2 esophageal adenocarcinoma cell lines. It was concluded that most of the digestive tract adenocarcinomas and a subset of their precursors express mucin 16. Mucin 16 expression is an independent predictor of poor outcome in pancreatic ductal adenocarcinomas and potentially in esophageal adenocarcinomas and gastric adenocarcinomas [250].

Myeloid-derived suppressor cells (MDCD)

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of immunosuppressive cells that are upregulated in cancer. Little is known about the prevalence and importance of MDSC in pancreas adenocarcinoma (PA). Peripheral blood, bone marrow, and tumor samples were collected from pancreatic cancer patients, analyzed for MDSC (CD15(+)CD11b(+)) by flow cytometry and compared to cancer-free controls. The suppressive capacity of MDSC (CD11b(+)Gr-1(+)) and the effectiveness of MDSC depletion were assessed in C57BL/6 mice inoculated with Pan02, a murine PA, and treated with placebo or zoledronic acid, a potent aminobisphosphonate previously shown to target MDSC. The tumor microenvironment was analyzed for MDSC (Gr1(+)CD11b(+)), effector T cells, and tumor cytokine levels. Patients with PA demonstrated increased frequency of MDSC in the bone marrow and peripheral circulation which correlated with disease stage. Normal pancreas tissue showed no MDSC infiltrate, while human tumors avidly recruited MDSC. Murine tumors similarly recruited MDSC that suppressed CD8(+) T cells in vitro and accelerated tumor growth in vivo. Treatment with zoledronic acid impaired intratumoral MDSC accumulation resulting in delayed tumor growth rate, prolonged median survival, and increased recruitment of T cells to the tumor. This was associated with a more robust type 1 response with increased levels of IFN-gamma and decreased levels of IL-10. MDSC are important mediators of tumor-induced immunosuppression in pancreatic cancer. Inhibiting MDSC accumulation with zoledronic acid improves the host anti-tumor response in animal studies suggesting that efforts to block MDSC may represent a novel treatment strategy for pancreatic cancer [251].

Osteopontins

Osteopontin (OPN) is a secreted protein of the extracellular matrix. It has been used as a marker for tumor aggressiveness and correlated with clinical outcomes in several solid tumors, such as liver, lung, and breast. It was determined the OPN expression and its influence on survival in patients with resected pancreatic adenocarcinoma. Tissue microarrays were constructed from 245 resected pancreatic adenocarcinomas. Immunohistochemical staining for OPN was undertaken and compared to normal pancreas (n=12). OPN expression was then correlated with patient demographics, tumor size, grade, node, and margin status. Survival curves were created by the Kaplan-Meier method and compared by log rank analysis. In total, 181 (74%) of pancreatic adenocarcinoma tissues expressed OPN compared to 7 (58 %) of normal controls, a significant difference. Expression was observed predominantly in the cytoplasm of the tumor cells. The median and 2 year overall survival was longer when OPN was expressed (17 vs 12 months, and 38 vs 24 %, respectively). Multivariate analysis showed OPN expression and T stage to be independent predictors of overall survival, while other histopathologic factors such as tumor grade, tumor size, and nodal status were not. These results suggest that the presence of OPN expression in pancreatic adenocarcinoma may have a protective effect independent of tumor stage. This emphasizes the importance of the interaction between pancreatic cancer cells and their stromal elements [252].

Poly-(ADP-ribose)-polymerases (PARPs)

High nuclear poly-(ADP-ribose)-polymerase expression is prognostic of improved survival in pancreatic cancer. Poly-(ADP-ribose)-polymerases (PARPs) act as post-translational modifiers of proteins that are mainly involved in the DNA repair machinery, and have recently been shown to be predictive of pathologically complete remission after chemotherapy in breast cancer. In the pancreas, PARP expression has so far only been studied in inflammatory conditions. Therefore, in one study, it was investigated the relevance of PARP in pancreatic cancer. Cytoplasmic and nuclear PARP expression was assessed by immunohistochemistry in a population-based cohort of 178 adenocarcinomas of the pancreas and correlated with clinicopathological parameters. It was found that low-level nuclear expression of PARP is associated with a poor prognosis (median survival 10 versus 15 months). The analysis shows that nuclear PARP is an independent prognostic marker with respect to standard clinicopathological parameters. These results suggest that PARP should be further explored as a predictive factor with respect to conventional chemotherapy and concepts of PARP inhibitor therapy in pancreatic cancer [253].

SLC5A8

One study aimed to assess the role of SLC5A8 expression in the survival of pancreatic cancer. It was determined SLC5A8 expression in pancreatic ductal adenocarcinoma and adjacent non-neoplastic pancreas obtained from 110 patients who underwent pancreatectomy. Formalin-fixed paraffin-embedded core sections in a tissue microarray were immunostained using polyclonal anti-SLC5A8 antibody, and a semiquantitative measure of SLC5A8 expression was determined. SLC5A8 expression was low in 56 percent (62/110) of pancreatic cancers as compared to non-neoplastic pancreas that had low expression in only 9 percent (10/107) of specimens. All cells expression of SLC5A8 did so in the cytoplasm, whether they are neoplastic or not. Nuclear expression of SLC5A8 occurred in 38 percent (42/110) of cancers, but it was uncommon in non-neoplastic pancreas (7 %, 8/107). Kaplan-Meier estimates showed that survival in patients whose cancers had low SLC5A8 expression, and/or nuclear expression, was significantly worse than in patients whose cancers had none of these abnormalities. For the 88 patients whose cancers had abnormal SLC5A8 expression, median survival was 1.4 years, as compared to 3.9 years in patients

whose cancers both expressed high levels of SLC5A8 and lacked nuclear expression. It was concluded that SLC5A8 nuclear translocation and loss of expression are associated with poor outcome in pancreatic ductal adenocarcinoma [254].

Smac and Ki-67

Tumors generally progress due to disruption in the balance between cellular proliferation and apoptosis. Thus, regulators of these processes tend to have altered expression in tumors, making them useful diagnostic and prognostic markers in the clinic. Here, it was explored the potential usefulness of proteins involved in each of these processes, Smac (apoptosis) and Ki-67 (proliferation), in pancreatic cancer. It was collected 35 pancreatic cancer samples and 12 normal pancreas samples and applied immunohistochemistry and pathology to determine the expression of these two proteins and their correlation with clinicopathology of the tumors. Both Smac (35/35) and Ki-67 (33/35) were significantly more highly expressed in pancreatic tumors than in normal pancreas (1/12 and 2/12, respectively). However, no correlation was detected between Smac and Ki-67 expression in these tumors. Importantly, Smac expression was correlated only with pathological grade, while Ki-67 expression was correlated only with pathological grade, while Ki-67 expression was correlated with pathological grade, lymph node metastasis, and clinical stage. The higher expression of Smac and Ki-67 appear to play a role in the pathogenesis of pancreatic cancer. Combined detection of these proteins may improve the prognostic evaluation of this disease [255].

Sonic hedgehog

Normally, sonic hedgehog (Shh) is expressed in the pancreas during fetal development and transiently after tissue injury. Although pancreatic cancers express Shh, it is not known if the protein is secreted into the blood and whether its plasma levels change with pancreatic transformation. The goal of this study was to develop an enzyme-linked immunosorbent assay to detect human Shh in blood and determine its levels in subjects with and without pancreatic cancer. A human Shh enzyme-linked immunosorbent assay was developed, and plasma Shh levels were measured in blood samples from healthy subjects and patients with pancreatitis or pancreatic cancer. The biological activity of plasma Shh was tested using NIH-3T3 cells. The mean levels of Shh in human blood were lower in patients with pancreatitis and pancreatic cancer than in healthy subjects. Hematopoietic cells did not express Shh, suggesting that Shh is secreted into the bloodstream. Plasma fractions enriched with Shh did not induce Gli-1 messenger RNA, suggesting that the protein was not biologically active. Shh is secreted from tissues and organs into the circulation, but its activity is blocked by plasma proteins. Reduced plasma levels were found in pancreatic cancer patients, but alone were not sufficient to predict pancreatic cancer [256].

Sleeping beauty mutagenesis

Human pancreatic cancer develops from preinvasive neoplasias, typically intraepithelial neoplasias (PanINs), although intraductal papillary mucinous neoplasia and mucinous cystic neoplasia can also give rise to adenocarcinoma. The majority of pancreatic adenocarcinoma is of ductal origin and contains a large desmoplastic component thought to promote tumorigenesis by modulating the tumor microenvironment. Oncogenic Kras mutations are found in 90 percent of human tumors, and they appear in early PanIN. The accumulation of additional inactivating driver mutations in P16/CDKN2A, TP53, and SMAD4 occurs with high frequency in later-stage PanIN, and these mutations are likely required for tumor progression to invasive adenocarcinoma. Recent high-throughput sequencing efforts have shown that the majority of somatic point mutations in primary pancreatic adenocarcinoma are missense mutations and that most occur at low frequency. Pancreatic cancers exhibit a very unstable genome, and through whole-genome sequencing efforts, a specific type of genomic

instability, termed fold-back inversion, has been elucidated. It is clear from these data that characterization of a large number of tumors is required to fully capture the molecular heterogeneity of the disease and identify the specific mutations and signaling pathways that drive disease progression. Pancreatic cancer has been successfully modeled in the mouse by driving expression of oncogenic Kras in the pancreas either alone or combined with inactivating alleles of homologs of known human pancreatic cancer drivers, including Smad4 and Trp53. All of these models show progressive neoplastic lesions, termed mPanIN, and develop locally invasive, and in some cases, metastatic ductal adenocarcinoma. Although these models have furthered our understanding of pancreatic cancer biology, new mutations that drive cancer development have not been uncovered in these efforts. The identification of molecular cancer drivers is critical for furthering our understanding of the disease and development of improved diagnostic tools and therapeutics. It was performed an insertional mutagenesis screen using the inducible Sleeping Beauty (SB) transposon system in combination with an oncogenic Kras pancreatic cancer model. This approach is a powerful means to identify mutations that cooperate with oncogenic Kras to drive tumorigenesis in the mouse, because each mutation is mapped using a transposon tag. Mice with SB insertional mutagenesis exhibit all stages of mPanIN lesions. SB decreases the latency of pancreatic tumorigenesis compared with oncogenic Kras alone and increases both the severity and multiplicity of ductal adenocarcinomas. Multiple metastases are also observed in a subset of animals. Using two independent statistical methods to identify loci commonly mutated by SB in these tumors, we identified 681 loci that comprise 543 candidate cancer genes (CCGs); 75 of these CCGs, including MII3 and Ptk2, have known mutations in human pancreatic cancer. We identified point mutations in human pancreatic patient samples for another 11 CCGs, including Acvr2a and Map2k4. Importantly, 10 percent of the CCGs are involved in chromatin remodeling, including Arid4b, Kdm6a, and Nsd3, and all SB tumors have at least one mutated gene involved in this process; 20 CCGs, including Ctnnd1, Fbxo11, and Vgll4, are also significantly associated with poor patient survival. SB mutagenesis provides a rich resource of mutations in potential cancer drivers for cross-comparative analyses with ongoing sequencing efforts in human pancreatic adenocarcinoma [257].

Superoxide

K-ras mutations have been identified in up to 95 percent of pancreatic cancers, implying their critical role in the molecular pathogenesis. Expression of K-ras oncogene in an immortalized human pancreatic ductal epithelial cell line, originally derived from normal pancreas (H6c7), induced the formation of carcinoma in mice. It was hypothesized that K-ras oncogene correlates with increased non-mitochondrial-generated superoxide (O_2) , which could be involved in regulating cell growth contributing to tumor progression. In the H6c7 cell line and its derivatives, H6c7er-Kras+ (H6c7 cells expressing K-ras oncogene), and H6c7eR-KrasT (tumorigenic H6c7 cells expressing K-ras oncogene), there was an increase in hydroethidine fluorescence in cell lines that express K-ras. Western blots and activity assays for the antioxidant enzymes that detoxify O2, were similar in these cell lines suggesting that the increase in hydroethidine fluorescence was not due to decreased antioxidant capacity. To determine a possible non-mitochondrial source of the increased levels of O2⁻ Western analysis demonstrated the absence of NADPH oxidase-2 (NOX2) in H6c7 cells but present in the H6c7 cell lines expressing K-ras and other pancreatic cancer cell lines. Inhibition of NOX2 decreased hydroethidine fluorescence and clonogenic survival. Furthermore, in the cell lines with the K-ras oncogene, overexpression of superoxide dismutases that detoxify non-mitochondrial sources of O₂, and treatment with the small molecule O₂ scavenger Tempol, also decreased hydroethidine fluorescence, inhibited clonogenic survival and inhibited growth of tumor xenografts. Thus, O_2 produced by NOX2 in pancreatic cancer cells with K-ras, may regulate pancreatic cancer cell growth [258].
Syndecan-2

It was identified syndecan-2 as a protein potentially involved in perineural invasion of pancreatic adenocarcinoma (PDAC) cells. Syndecan-2 (SDC-2) expression was analyzed in human normal pancreas, chronic pancreatitis and PDAC tissues. Functional in vitro assays were carried out to determine its role in invasion, migration and signaling. SDC-2 was expressed in the majority of the tested pancreatic cancer cell lines while it was upregulated in nerve-invasive PDAC cell clones. There were 2 distinct expression patterns of SDC-2 in PDAC tissue samples: SDC-2 positivity in the cancer cell cytoplasm and a peritumoral expression. Though SDC-2 silencing (using specific siRNA oligonucleotides) did not affect anchorage-dependent growth, it significantly reduced cell motility and invasiveness in the pancreatic cancer cell lines T3M4 and Su8686. On the transcriptional level, migration-and invasion-associated genes were down-regulated following SDC-2 RNAi. Furthermore, SDC-2 silencing reduced K-ras activity, phosphorylation of Src and – further downstream – phosphorylation of ERK2 while levels of the putative SDC-2 signal transducer p120GAP remained unaltered. It was concluded that SDC-2 is a novel (perineural) invasion-associated gene in PDAC which cooperates with K-ras to induce a more invasive phenotype [259].

Tregs

Regulatory T cells (Treg) can inhibit immune responses mediated by T cells. The aim of one study was to evaluate the prevalence of Treg in peripheral blood mononuclear cells from patients with pancreatic cancers in relation to their clinical outcomes. Among a total of 100 patients with ductal adenocarcinoma of the pancreas, 40 underwent pancreatectomy and 60 had unresectable disease. Their peripheral blood mononuclear cells were evaluated to determine the proportion of CD4CD25 (FoxP3) T cells, as a percentage of the total CD4 cells, by flow cytometric analysis. The percentage of Treg in the patients with pancreatic cancer was significantly lower than that in the healthy volunteers, and the patients who underwent surgical resection had lower Treg levels than those with unresectable disease. Patients in the resected group with a higher percentage of Treg survived longer. Treg in patients who remained disease free at postoperative 12 months significantly decreased compared to that of the postoperative period. A relative increase in Treg may be related to immunosuppression and tumor progression in patients with pancreatic cancer. The immunological monitoring of Treg may be useful to predict the prognosis for patients with pancreatic cancer [260].

Tumor-associated macrophages (TAMs)

The histologic presence of macrophages (tumor-associated macrophages, TAMs) and neutrophils (tumor-associated neutrophils, TANs) has been linked to poor clinical outcomes for solid tumors. The exact mechanism for this association with worsened prognosis is unclear. It has been theorized that TAMs are immunomodulated to an alternatively activated state and promote tumor progression. Similarly, TANs have been shown to promote angiogenesis and tumor detachment. TAMs and TANs were characterized for activation state and production of prometastatic mediators in an immunocompetent murine model of pancreatic adenocarcinoma. Specimens from liver metastases were evaluated by immunofluorescence and immunoblotting. TAMS have upregulated expression of CD206 and CD163 markers of alternative activation, (4.14 ± 0.55-fold and 7.36 ± 1.13-fold over control, respectively) but do not have increased expression of classically activated macrophage markers CCR2 and CCR5. TAMs also express oncostatin M (OSM). We found that TANs, not TAMs, predominantly produce matrix metalloproteinase-9 (MMP-9) in this metastatic tumor microenvironment, while MMP-2 production is pan-tumoral. Moreover, increased expression of VEGF colocalized with TAMs as opposed to TANs. TAMs and TANs may act as distinct effector cells, with TAMs phenotypically exhibiting alternative activation and

releasing OSM and VEGF. TANs are localized at the invasive front of the metastasis, where they colocalize with MMP-9. Improved understanding of these interactions may lead to targeted therapies for pancreas adenocarcinoma [261].

Biomarkers for pancreatic cancer

The identification of new biomarkers for preneoplastic pancreatic lesions (PanINs, IPMNs) and early pancreatic ductal adenocarcinoma (PDAC) is crucial due to the diseasés high mortality rate upon late detection. To address this task we used the novel technique of matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) on genetically engineered mouse models (GEM) of pancreatic cancer. Various GEM were analyzed with MALDI IMS to investigate the peptide/protein-expression pattern of precursor lesions in comparison to normal pancreas and PDAC with cellular resolution. Statistical analysis revealed several discriminative m/z-species between normal and diseased tissue. Intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) could be distinguished from normal pancreatic tissue and PDAC by 26 significant m/z-species. Among these m/z-species, it was identified albumin and thymosin-beta 4 by liquid chromatography and tandem mass spectrometry (LC-MS/MS), which were further validated by immunohistochemistry, western blot, quantitative RT-PCR and ELISA in both murine and human tissue. Thymosin-beta 4 was found significantly increased in sera of mice with PanIN lesions. Upregulated PanIN expression of albumin was accompanied by increased expression of liver-restricted genes suggesting a hepatic transdifferentiation program of preneoplastic cells. In conclusion it was shown that GEM of endogenous PDAC are a suitable model system for MALDI-IMS and subsequent LC-MS/MS analysis, allowing in situ analysis of small precursor lesions and identification of differentially expressed peptides and proteins [262].

Late diagnosis of pancreatic ductal adenocarcinoma (pancreatic cancer) and the limited response to current treatments result in an exceptionally poor prognosis. Advances in our understanding of the molecular events underpinning pancreatic cancer development and metastasis offer the hope of tangible benefits for patients. In-depth mutational analyses have shed light on the genetic abnormalities in pancreatic cancer, providing potential treatment targets. New biological studies in patients and in mouse models have advanced our knowledge of the timing of metastasis of pancreatic cancer, highlighting new directions for the way in which patients are treated. Furthermore, our increasing understanding of the molecular events in tumorigenesis is leading to the identification of biomarkers that enable us to predict response to treatment. A major drawback, however, is the general lack of an adequate systematic approach to advancing the use of biomarkers in cancer drug development, highlighted in a Cancer Biomarkers Collaborative consensus report. In this Review, we summarize the latest insights into the biology of pancreatic cancer, and their repercussions for treatment. It was provide an overview of current treatments and, finally, it was discussed novel therapeutic approaches, including the role of biomarkers in therapy for pancreatic cancer [263].

Other (traditional) tumor markers

CA19-9 is the most specific biomarker for pancreas cancer. It was investigated the prognostic significance of normal (\leq 37 U/mL) versus elevated (> 37 U/mL) CA19-9 levels in patients with resected and advanced pancreas cancer. Relevant data were obtained from patients treated for early-stage or advanced pancreatic adenocarcinoma at our institution. Log-rank tests were used to evaluate relationship between CA19-9 and clinical outcomes of interest for both early- and advanced-stage patients. A total of 123 patients were included

(Group A: n=30 stage I/II; Group B: n=93 stage III/IV). In group A, elevated preoperative CA19-9 was significantly associated with lymph node involvement, tumor \geq 3 cm, and lack of tumor differentiation. Failure of postoperative CA19-9 to normalize predicted significantly worse DFS. For group B, elevated baseline CA19-9 was associated with shorter OS on chemotherapy and decline in CA19-9 >25 percent with treatment was a significant predictor of improved OS. Higher than normal CA19-9 level is an adverse prognostic factor in both early and advanced settings and may prove to be useful in the selection of patients for more aggressive therapy in future trials. CA19-9 level decrease of >25 percent predicts improved survival in advanced disease on chemotherapy [264].

Experimental

Influence of stress

Pancreatic cancer has a poor prognosis and is associated with high levels of psychological stress that may adversely affect clinical outcomes. However, the potential influence of neuropsychological factors on pancreatic cancer has not been investigated to date. Using a mouse model of social stress, it was tested the hypothesis that psychological stress promotes the progression of pancreatic cancer xenografts via neurotransmitter-induced activation of multiple pathways and that the inhibitory neurotransmitter gamma-aminobutiric acid (GABA) inhibits these responses. Sytemic and xenograft levels of noradrenalin, adrenalin, GABA, cortisol, vascular endothelial growth factor (VEGF) and cyclic adenosine 3', 5'-monophosphate (cAMP) were measured by immunoassays. Xenograft expression of nicotinic acetylcholine receptors (nAChRs) alpha3, alpha4, alpha5, alpha6 and alpha7 and beta-adrenergic receptors 1 and 2 were assessed by real-time PCR and western blots. Expression of glutamate decarboxylases GAD65 and GAD67 and phosphorylated and unphosphorylated signaling proteins of relevance to pancreatic cancer were determined in tumor tissue by western blots. Psychological stress significantly promoted xenograft growth and increased systemic and tumor levels of noradrenalin, adrenalin, cortisol, VEGF and cAMP while GABA and GAD were suppressed. Stress upregulated nAChR proteins but not RNAs and induced phosphorylated ERK, CREB, Src and AKT in xenografts. Reduction of cAMP by treatment with GABA prevented tumor progression and activation of signaling proteins. The findings suggest that neurotransmitter responses to psychological stress negatively impact clinical outcomes of pancreatic cancer via the activation of multiple pathways and that replacement of the suppressed inhibitory neurotransmitter GABA prevents these effects [265].

Genetics

Pancreatic has the poorest prognosis of any major tumor type, with a 5-year survival rate of approximately 5 percent. A family history of pancreatic cancer has been associated with increased risk suggesting inherited genetic factors also play an important role, with approximately 5-10 percent of pancreatic cancer patients reporting family history of pancreatic cancer. While the genetic basis for the majority of the familial clustering of pancreatic cancer remains unclear, several important pancreatic cancer genes have been identified. These consist of high penetrance genes including BRCA2 or PALB2, to more common genetic variation associated with a modest increase risk of pancreatic cancer such as genetic variation at the ABO blood group locus. Recent advances in genotyping and genetic sequencing have accelerated the rate at which novel pancreatic cancer susceptibility genes have been identified with several genes identified within the past few years. One review addressed the current understanding of the familial aggregation of pancreatic cancer,

established pancreatic cancer susceptablity genes and how this knowledge informs risk assessment and screening for high-risk families [266].

BRCA1 and BRCA2

Germline mutations in the BRCA2 cancer susceptibility gene are associated with an increased risk of pancreatic cancer (PC). Breast-pancreas cancer families with BRCA1 mutations have also been observed. The influence of a family history (FH) of PC on BRCA mutation prevalence in patients with breast cancer (BC) is unknown. A clinical database review (2000-2009) identified 211 Ashkenazi Jewish (AJ) BC probands who 1) underwent BRCA1/2 mutation analysis by full gene sequencing or directed testing for Ashkenazi founder mutations (BRCA1: 185delAG and 5382insC; BRCA2: 6174delT) and 2) had a FH of PC in a first-, second-, or third-degree relative. For each proband, the pretest probability of identifying a BRCA1/2 mutation was estimated using the Myriad II model. The observed-to-expected (O:E) mutation prevalence was calculated for the entire group. Of the 211 AJ BC probands with a FH of PC, 30 (14 %) harbored a BRCA mutation. Fourteen (47 %) of the mutations were in BRCA1 and 16 (53 %) were in BRCA2. Patients diagnosed with BC at age \leq 50 years were found to have a higher BRCA1/2 mutation prevalence than probands with BC who were diagnosed at age > 50 years (21 % vs 7 %). In patients with a first-, second-, or third-degree relative with PC, mutation prevalences were 15 percent, 15 percent, and 9 percent, respectively. In the overall group, the observed BRCA1/2 mutation prevalence was 14 percent versus an expected prevalence of 12 percent (O:E ratio, 1.21). It was concluded that BRCA1 and BRCA2 mutations are observed with nearly equal distribution in AJ breastpancreas cancer families, suggesting that both genes are associated with PC risk. In this population, a FH of PC was found to have a limited effect on mutation prevalence [267].

PRSS1

Genetic risk factors of chronic pancreatitis (CP) have been identified and a number of studies have found that CP can lead to pancreatic cancer. Therefore, the detection of pancreatitisassociated gene mutations can aid the pancreatic cancer diagnostic process. Mutations in three genes, the cationic trypsinogen (PRSS1) gene, the cystic fibrosis transmembrane conductance regulator (CFTR) gene and the pancreatic secretory trypsin inhibitor (SPINK1) gene, have been identified as risk factors for CP. The aim of one study was to describe specific novel mutations in the intron of the PRSS1 gene in patients with pancreatic cancer and CP. A total of 65 unrelated patients with pancreatic cancer and 29 with CP were reviewed. Mutations and polymorphisms of the PRSS1 gene were analyzed by direct sequencing. Information regarding clinical data and smoking exposure was collected by personal interviews using a structured questionnaire. IVS 3+36 A>G mutation in the PRSS1 gene was found in 2 cases with pancreatic cancer, and these 2 patients were classified as never-smokers. IVS 3+127 T>A and IVS 3+157 G>C double mutations were identified in one patient with CP. All patients were found to have serum trypsin levels lower than that of the normal controls. Therefore, the PRSS1 gene mutation may be a special common cause of pancreatic cancer and CP [268].

ABO-groups

Thirty years of research with animal models has shown that pancreatic adenocarcinoma is induced by N-nitrosamine carcinogens, which damage DNA through adduct formation. Human risk factors for pancreatic cancer include gastric colonization by Helicobacter pylori, as well as dietary intake of those same N-nitrosamines or of nitrite which forms those N-nitrosamines in the stomach, and cigarette smoking which also contains those N-nitrosamines. Physiologic actions of H. pylori colonization enhance the carcinogenic effect of N-nitrosamines delivered by smoking or dietary sources. This effect is modulated by host

inflammatory response to the organism, by various virulence and other properties of the Helicobacter itself, and by host-organism interactions. A recent genome-wide association study identified SNPs within the ABO 9q34 locus as statistically significantly associated with risk of pancreatic cancer. A number of recent and older studies going back 40 years also support the ABO association. ABO-product antigens are expressed on gastrointestinal epithelium on which H. pylori binds, and ABO genotype is known to be associated with risks of duodenal and gastric ulcer and with risk of gastric cancer, conditions definitively related to Helicobacter colonization. It is suspected that ABO genotype/phenotype status influences the behavior of H. pylori which in turn affects gastric and pancreatic secretory function, and these ultimately influence the pancreatic carcinogenicity of dietary- and smoking-related N-nitrosamine exposures, and thus risk of pancreatic cancer. Our study results on the interaction of ABO and H. pylori significantly confirm this hypothesis and together with other existing studies strongly implicate this organism in the disease etiology [269].

6q13

Copy number variations (CNVs) have been recognized to contribute to phenotypic variations and to be associated with susceptibility to certain complex diseases. One study examined the functional significance of CNVR2966.1 at 6q13 and its association with pancreatic cancer susceptibility. The CNVR2966.1 was found to be a 10,379 bp nucleotides deletion/insertion within the uniform boundaries chromosome 6: 74 648 791-74 659 169. Luciferase reporter gene assays revealed an active regulator in CNVR2966.1, which was demonstrated by circular chromosome conformation capture assays to physically interact with the upstream functional sequence of CDKN2B. CDKN2B transcription levels in pancreatic tissues were therefore significantly higher in individuals with two copies of CNVR2966.1 than in those with low copy number of CNVR2966.1. The risk of pancreatic cancer observed in 1027 cases and 1031 controls was significantly associated with copy number of CNVR2966.1, with the odds ratio being 1.31 for one copy genotype compared with two copies genotype. These results suggest that CNVR2966.1 is associated with pancreatic cancer risk probably owing to its effect on long-range regulation of CDKN2B [270].

Histopathology

Most solid pancreatic tumors are invasive ductal adenocarcinoma (PDAC). Because PDAC is the most common tumor, it has become synonymous with the term "pancreas cancer." However, other malignant neoplasms occur in the pancreas (acinar, neuroendocrine and colloid carcinomas, and metastases) all with different outcomes. Because these tumors are often combined with PDAC in research databases, it causes misleading variability in the analysis of pancreatic cancers. It was examined the histopathology of a variety of pancreatic cancers [271].

On the origin of "ductular" cancer

Pancreatic ductal adenocarcinoma (PDAC) has long been considered to arise from pancreatic ducts on the basis of its morphology, the occurrence of dysplasia in putative preneoplastic ductal lesions, and the absence of acinar dysplasia in the pancreas of patients with PDAC. However, evidence gathered through both in vitro studies and – more importantly – genetic mouse models of PDAC shows that ductal-type tumours can arise from acinar cells. These findings raise new important questions related to PDAC pathophysiology and call for in-depth studies of acinar cell differentiation in order to better understand PDAC biology. The authors reviewed these issues and discuss how the novel findings should impact on future work aiming at early diagnosis and improved outcome of patients with PDAC [272].

Pancreatic ductal adenocarcinoma (PDAC) and its precursor lesions, pancreatic intraepithelial neoplasia (PanIN), display a ductal phenotype. However, there is evidence in genetically defined mouse models for PDAC harbouring a mutated Kras under the control of a pancreas-specific promoter that ductal cancer might arise in the centroacinar-acinar region, possibly through a process of acinar-ductal metaplasia (ADM). In order to further elucidate this model of PDAC development, an extensive expression analysis and molecular characterization of the putative and already established (PanIN) precursor lesions were performed in the Kras(G12D/+); Ptf1a-Cre(ex1/+) mouse model and in human tissues, focusing on lineage markers, developmental pathways, cell cycle regulators, apomucins, and stromal activation markers. The results of one study show that areas of ADM are very frequent in the murine and human pancreas and represent regions of increased proliferation of cells with precursor potential. Moreover, atypical flat lesions originating in areas of ADM are the most probable precursors of PDAC in the Kras(G12D/+); Ptf1a-Cre(ex1/+) mice and similar lesions were also found in the pancreas of three patients with a strong family history of PDAC. In conclusion, PDAC development in Kras(G12D/+); Ptf1a-Cre(ex1/+) mice starts from ADM and a similar process might also take place in patients with a strong family history of PDAC [273].

Post-therapy pathologic stage

Neoadjuvant chemoradiation before surgery is an emerging treatment modality for pancreatic ductal adenocarcinoma (PDAC). However, analysis of prognostic factors is limited for patients with PDAC treated with neoadjuvant chemoradiation and pancreaticoduodenectomy (PD). The study population was comprised of 240 consecutive patients with PDAC who received neoadjuvant chemoradiation and PD and was compared with 60 patients who had no neoadjuvant therapy between 1999 and 2007. Clinicopathologic features were correlated with disease-free survival (DFS) and overall survival (OS). Among the 240 treated patients, the 1-year and 3-year DFS rates were 52 and 32 percent, with a median DFS of 15 months. The 1-year and 3-year OS rates were 95 and 47 percent, with a median OS of 34 months. By univariate analysis, DFS was associated with age, post-therapy tumor stage (ypT), lymph node status (ypN), number of positive lymph nodes, and American Joint Committee on Cancer (AJCC) stage, whereas OS was associated with intraoperative blood loss, margin status, ypT, ypN, number of positive lymph nodes, and AJCC stage. By multivariate analysis, DFS was independently associated with age, number of positive lymph nodes, and AJCC stage, and OS was independently associated with differentiation, margin status, number of positive lymph nodes, and AJCC stage. In addition, the treated patients had better OS and lower frequency of lymph node metastasis than those who had no neoadjuvant therapy. It was concluded that in patients with PDAC who received neoadjuvant chemoradiation and subsequent PD, post-therapy pathologic AJCC stage and number of positive lymph nodes are independent prognostic factors [274].

Morphometrical differences

Pancreatic cancer is a highly aggressive cancer with a rising incidence and poor prognosis despite active surgical treatment. Candidates for surgical resection should be carefully selected. In order to avoid unnecessary laparotomy it is useful to identify reliable factors that may predict resectability. Nuclear morphometry and fractal dimension of pancreatic nuclear features could provide important preoperative information in assessing pancreas resectability. Sixty-one patients diagnosed with pancreatic cancer were enrolled in this retrospective study between 2003 and 2005. Patients were divided into two groups: one resectable cancer group and one with non-resectable pancreatic cancer. Morphometric parameters measured were: nuclear area, length of minor axis and length of major axis. Nuclear shape and chromatin distribution of the pancreatic tumor cells were both estimated

using fractal dimension. Morphometric measurements have shown significant differences between the nuclear area of the resectable group and the non-resectable group (62 ± 20 microm vs 42 ± 16 microm). Fractal dimension of the nuclear outlines and chromatin distribution was found to have a higher value in the non-resectable group. Objective measurements should be performed to improve risk assessment and therapeutic decisions in pancreatic cancer. Nuclear morphometry of the pancreatic nuclear features can provide important pre-operative information in resectability assessment. The fractal dimension of the nuclear shape and chromatin distribution may be considered a new promising adjunctive tool for conventional pathological analysis [275].

Borderline cases

Because less than 20 percent of patients with pancreatic cancer are candidates for surgery, another treatment strategy is to treat patients with borderline resectable disease in an attempt to make the tumors resectable. There is a subset of about 7 percent of patients who do not have evidence of metastatic disease but do have locally aggressive disease and fall into the borderline resectable category. Recent efforts have been undertaken to treat patients with borderline resectable tumors with an intention to increase the number of R0 resections. Currently, the National Comprehensive Cancer Network guidelines include optional recommendations for neoadjuvant therapy in cases of borderline resectable tumors but recommend enrollment in clinical trials for patients desiring neoadjuvant therapy who have resectable disease. Many groups have studied the clinical effectiveness of various preoperative chemotherapies and radiation therapy regimens. Chemotherapy agents that have been used include gemcitabine, 5-fluorouracil, mitomycin C, platinum compounds, and paclitaxel, and the list continues to grow. Absorbed radiation doses (absorbed per unit of body weight of tissue) to the pancreas typically range from 30 to 60 Gy. In addition to making unresectable tumors resectable, the benefits of preoperative, neoadjuvant chemoradiation therapy over adjuvant chemoradiation therapy include

- obtaining a higher percentage of negative surgical margins
- targeting tissue that is presumed to be well perfused, leading to more effective chemotherapy effect
- avoiding a fixed bowel within the radiation field
- improved tolerance of chemoradiation before a large, complex surgery

Although the clinical effectiveness and outcomes data related to these various chemoradiation therapy regimens have been reported, few studies have looked at the histologic effects related to therapy. Given the current medical culture of outcomes-based medicine, as well as the uncertainty concerning the optimal therapeutic modality, several outcomes have been used to evaluate the therapeutic effect of treatment in pancreatic cancer. These have included clinical measures (symptoms/laboratory value improvement or laparoscopic assessment), radiologic measures (tumor size by endoscopic ultrasound, computed tomographic scan, or magnetic resonance imaging), and pathologic measures. The College of American Pathologists' Protocol for the Examination of Specimens From Patients With Carcinoma of the Exocrine Pancreas currently recommends that tumor response to previous chemotherapy and/or radiation therapy be reported. Although the protocol acknowledges that grading systems for tumor response have not been well established, the following tumor regression grading system is recommended: grade 0, complete response (no viable cancer cells); grade 1, moderate response (single cells or small groups of cancer cells); grade 2, minimal response (residual cancer outgrown by fibrosis); and grade 3, poor response (minimal or no tumor kill; extensive residual cancer). The protocol also states that other systems for assessment of tumor response can be used [179].

Grading the histopathologic response to preoperative chemoradiation therapy

A few histopathologic schemes for grading response to therapy in pancreatic cancer have been proposed. In 1989, Ishikawa et al assessed radiation treatment effect based on radiologic imaging and histologic findings. Histologically, they examined the amount of severely degenerative cancer cells (SDCC) in a series of 18 patients (12 pancreatic, 4 biliary, and 2 ampullary cancers). By their criteria, SDCC had either (1) absent, pyknotic, or irregular-shaped nuclei, or (2) acidophilic or vacuolated cytoplasm. Treatment effect was separated into 3 categories: (1) one-third or less of the cancer cell population represented SDCCs, (2) between one-third and two-thirds of cancer cell population represented SDCCs, and (3) greater than two-thirds of the cancer cell population represented SDCCs. These histologic categories correlated with posttherapy radiologic imaging. Additionally, the authors described 3 histologic patterns: type A, predominantly fibrosis with a few SDCCs, but nonaffected cancer cells undetected; type B, a fibrous connective tissuelike capsule (1-3 mm thick), with predominantly SDCCs at the periphery of the lesion and nonaffected cancer cells in the center; and type C, SDCCs randomly distributed within nonaffected cancer cells. The difference between these histologic patterns correlated with the percentage of SDCCs. Interestingly, in a clinical trial reporting response to neoadjuvant therapy, nearly 77% of the cases met the type A histologic pattern. The main outcomes of the Ishikawa et al study were based on operative parameters (a low anastomotic leak rate, no operative mortality, all patients underwent surgery, and less morbidity than a control population of patients not given radiation therapy) and showed that the preoperative radiation was well tolerated. The limited survival data in the initial study reported only one death from cancer 12 months after operation (follow-up period was between 2 and 39 months). In the clinical trial that used the Ishikawa et al grading scheme, 13 of 26 cases (50 %) demonstrated greater than 80 percent SDCCs (defined as a major response according to the clinical trial), but the assessment of histologic response was not associated with overall or disease-free survival. A local relapse was reported in one patient from the clinical trial who had negative resection margins after neoadjuvant therapy, and that patient lacked evidence of a histologic response. The Evans et al grading scheme for determining treatment effect is the most widely used. This scheme is based on grading response to therapy in other organ systems. This grading scheme consists of a 4-tiered system that assesses the percentage of viable cells remaining in the lesion, with the lowest grade (grade I) representing little or no response (<10 % to no tumor cells destroyed) and the highest grade (grade IV) representing the greatest response (no viable tumor cells or acellular pools of mucin); grades II and III represent a spectrum of tumor cell destruction from 10 percent to more than 90 percent tumor cells destroyed. The authors felt that necrosis, especially coagulative necrosis, could not be interpreted as evidence of treatment effect because it is commonly observed in untreated tumors. In practice, although the detection of residual tumor cells is typically straightforward, determining the viability of these cells based on histomorphologic features can be quite challenging, if not impossible [179].

According to the grading scheme proposed by Evans et al viable pancreatic cancer cells can show cytoplasmic or nuclear swelling, multiple nuclei, and cytoplasmic vacuolization, whereas nonviable cancer cells have bizarre, hyperchromatic, pyknotic nuclei usually with swollen, vacuolated, or deeply eosinophilic cytoplasm and exhibit karyorrhexis. Because neither illustrations nor photomicrographs of tumor cell destruction have been published, aside from one photomicrograph of SDCCs in the Ishikawa paper, defining cells as viable or nonviable is purely subjective and potentially prone to significant interoberserver and intraobserver variability. This is problematic when attempting to use a grading scheme that includes viability. For example, if a few tumor cells remain, the distinction between an Evans et al grade III and grade IV response will depend on the viability of the cells. If the cells are deemed nonviable, it is a grade IV response, but if they are deemed viable, then the response is grade III. Most patients evaluated by the Evans et al grading scheme in published reports have fallen into the grade II or grade III category; only a handful of patients in the studies reviewed were reported to have a complete (grade IV) response to preoperative chemoradiation therapy. One study that correlated histologic response to outcome showed that patients whose tumors demonstrated minimal pathologic effect from neoadjuvant therapy (score IIa) had more than twice the risk of death as did patients with a partial or complete pathologic response (score IIb, III, or IV) (hazard ratio, 2.74). Although treatment effect was found to be associated with overall survival, the authors could not be confident that treatment effect can predict survival because the number of patients in this study was too small. In another study, the histologic assessment of treatment effect did not correlate with survival duration by multivariate analysis [179].

Another scheme for grading response to chemoradiation has been proposed by Pendurthi et al. They presented their grading scheme at a meeting of the American Gastroenterological Association in 1996, and this scheme has been used by some authors to assess therapy effect. Per the meeting abstract, this scheme assessed 3 histologic features: (1) the ratio of tumor cells to fibrosis, (2) the percentage of either liquefactive or coagulative necrosis in the tumor, and (3) the presence of treatment effect. Characteristics cited as indicative of treatment effect included (1) nuclear gigantism, (2) hypereosinophilic cytoplasm, (3) vacuolated cytoplasm, (4) nuclear dropout and/or degeneration, and (5) cell dropout. In the study analyzing histopathologic outcome after preoperative therapy, multiple sections representing all areas of the tumor were examined, and the fibrosis level was reported as the mean value for the tumor. In that study, patients with a significant response to therapy, defined as a ratio of fibrosis to tumor greater than or equal to 80 percent, had fewer positive margins and fewer positive lymph nodes, but on multivariate analysis, the percentage of fibrosis alone did not affect survival. Another study using this grading scheme found that, in patients who lived longer than 3 years, 3 out of 4 (75 %) showed at least 75 percent tumor replacement [179].

White et al created a grading scheme that combined the Pendurthi et al and Evans et al grading schemes. They modified the fibrosis assessment by categorizing it into 3 grades: mild, moderate, and extensive. Additionally, they examined the presence of necrosis within the tumors. The definition provided by the authors was "lysed cells with necrotic debris." This assessment is in contrast to the Evans et al scheme, which specifically excluded necrosis. Necrosis was assessed as extensive, moderate, focal, or absent, and the presence of necrosis was found to be a worse prognostic factor. For the final assessment, the authors estimated the extent of the tumor mass occupied by residual, viable tumor cells. A large tumor load (>90 % viable, which is equivalent to <10 % destruction or Evans et al grade I) and the presence of tumor necrosis were both worse prognostic factors. Fibrosis was not associated with survival by either univariate or multivariate analysis [179].

Limitations with these grading schemes

Aside from the inherent variability among observers, the application of these schemes in clinical studies has been somewhat inconsistent compared with the original articles. For instance, some studies adjust the level of fibrosis that is considered significant, whereas other studies adjust the cutoff for SDCCs or interpret necrosis as evidence of treatment effect. In fact, there is limited data to suggest that any of these grading schemes correlate with patient outcomes. Essentially, the grading schemes are reduced to measuring one of the 3 variables: viable tumor cell mass, fibrosis, and/or necrosis. Tumor cell mass histologic finding correlated with shrinkage in tumor size by radiologic imaging but does not correlate with outcomes. It is unclear whether the assessment of treatment effect for head and neck cancers (usually squamous cell lesions) applies to pancreatic cancer (usually glandular lesions). Viable cells are described as those cells "whose morphologic features were fairly well-preserved, including those with swelling of the nucleus or cytoplasm, multiple nuclei, or cytoplasmic vacuolation." Changes considered irreversible included "cells with bizarre, hyperchromatic, or pyknotic nuclei, usually associated with markedly swollen, vacuolated, or deeply eosinophilic cytoplasm." Karyorrhexis was considered a sign of cell death, but whether this occurs in untreated cancers was not discussed. No study has examined these histologic variables of viability, tumor load, and necrosis to assess whether they are inherent to the neoplastic process or to the neoadjuvant therapy. Also, to date, no guidelines for distinguishing tumor-generating, desmoplastic fibrosis from therapy-induced fibrosis have been proposed. Additionally, in pancreatic cancer, the background pancreatic parenchyma frequently shows fibrosis from the obstructive effect of the lesion. The most significant factor that predicted the radioresistance, especially at the periphery of the carcinoma, was the presence of coexisting chronic pancreatitis. On the other hand, some pancreatic cancers also elicit no desmoplastic response. These differences in the presentation of pancreatic cancer likely represent underlying differences in biology that are as yet not understood. From a clinical perspective, pancreatic cancer is often initially diagnosed based on fine-needle aspiration, precluding evaluation of the architecture in which the pancreatic cancer is situated (whether the neoplastic cells are eliciting a fibrotic response or not). Therefore, determining the response to therapy in patients with pancreatic cancer is extremely challenging. Another controversial area in assessing the therapy effect is the significance of necrosis. A confusing issue that further makes the application of these grading schemes challenging is the inconsistency in the literature regarding the assignment of grade to treated cancers throughout the gastrointestinal tract. The College of American Pathologists recommends the use of a 4-tier system for assessing tumor response to previous chemotherapy and/or radiation therapy. For presumed ease and consistency, the College of American Pathologists recommended the same grading system for all pancreatic and gastrointestinal cancers for which neoadjuvant therapy may apply and assigned the best (most complete) response to the lowest grade (grade 0) [179].

Precancerous lesions

Pancreatic ductal adenocarcinoma (PDAC) and its precursor lesions, pancreatic intraepithelial neoplasia (PanIN), display a ductal phenotype. However, there is evidence in genetically defined mouse models for PDAC harbouring a mutated kras under the control of a pancreas-specific promoter that ductal cancer might arise in the centroacinar-acinar region. possibly through a process of acinar-ductal metaplasia (ADM). In order to further elucidate this model of PDAC development, an extensive expression analysis and molecular characterization of the putative and already established (PanIN) precursor lesions were performed in the Kras(G12D/+); Ptf1a-Cre(ex1/+) mouse model and in human tissues, focusing on lineage markers, developmental pathways, cell cycle regulators, apomucins, and stromal activation markers. The results of this study show that areas of ADM are very frequent in the murine and human pancreas and represent regions of increased proliferation of cells with precursor potential. Moreover, atypical flat lesions originating in areas of ADM are the most probable precursors of PDAC in the Kras(G12D/+); Ptf1a-Cre(ex1/+) mice and similar lesions were also found in the pancreas of three patients with a strong family history of PDAC. In conclusion, PDAC development in Kras(G12D/+); Ptf1a-Cre(ex1/+) mice starts from ADM and a similar process might also take place in patients with a strong family history of PDAC [276].

Nonlinear optical methods

Nonlinear optical methods based on two-photon excited fluorescence (TPEF) and second harmonic generation (SHG) of intrinsic optical biomarkers show the ability to visualize the morphology of fresh tissues associated with histology, which is promising for real-time intraoperative evaluation of pancreatic cancer. Optical methods, taking advantage of non-invasion and high tempo-spatial resolution, can achieve in vivo imaging and sensing in biomedical studies. Raman spectroscopy, which is based on the difference in the energy of the incident and scattered photons due to the molecular vibrations, is sensitive to the changes of chemical composition in cells and tissues. It has been applied to the differentiation of normal and cancerous pancreatic tissues from a mouse model. Reflectance and fluorescence spectroscopy can provide biochemical information of the tissues to

distinguish different human pancreatic tissues, including normal pancreatic tissue, pancreatitis, and pancreatic adenocarcinoma. Photon-tissue interaction models have been further developed to provide quantitative links between the reflectance and fluorescence measurements and histological characteristics of human pancreatic tissues, such as the nuclear size. However, the spectral parameters are difficult to be directly matched with the morphological features revealed by the conventional histological examination, especially the changes of nuclear shape and organization of the extracellular matrix. More detailed characterization of the pancreatic morphology with cellular resolution using optical methods is necessary to improve the detection of pancreatic neoplasia, implicating a new means of real-time histology. In recent years, nonlinear optical microscopy (NOM), primarily including TPEF and SHG, has emerged as a powerful tool to identify slight structural and functional changes at cellular resolution. NOM has the advantage of submicron spatial resolution. millisecond temporal resolution, and the optical sectioning ability in turbid tissue. One important nature of such an imaging modality is that the endogenous optical biomarkers in tissues can be employed to provide contrast, which makes it possible to detect human diseases without the need for fixation, sectioning, or staining. Intrinsic two-photon excited fluorescence (TPEF) biomarkers including reduced nicotinamide adenine dinucleotide (phosphate), NAD(P)H, and flavin adenine dinucleotide (FAD) have been applied to reveal the morphology of the cells, since NAD(P)H and FAD are the major fluorophores in the cytoplasm. Meanwhile, the collagen fibers, which are important structural proteins in the extracellular matrix (ECM), can implement the intrinsic second harmonic generation (SHG) process in biological tissues to reflect the ECM pattern. In addition, the intracellular NAD(P)H and FAD are also related with the redox ratio of cells, which can be used as an indicator of the metabolic level of cells. NOM has been widely applied to visualize cellular and tissue structures in different cancer tissues including ovarian, bladder, gastric tissues, and so on. In order to investigate whether the nonlinear optical imaging methods have the ability to characterize pancreatic histology at cellular resolution, it was studied different types of pancreatic tissues by using label-free TPEF and SHG. Compared with other routine methods for the preparation of specimens, fresh tissues without processing were found to be most suitable for nonlinear optical imaging of pancreatic tissues. The detailed morphology of the normal rat pancreas was observed and related with the standard histological images. Comparatively speaking, the preliminary images of a small number of chemical-induced pancreatic cancer tissues showed visible neoplastic differences in the morphology of cells and extracellular matrix. The subcutaneous pancreatic tumor xenografts were further observed using the nonlinear optical microscopy, showing that most cells are leucocytes at 5 days after implantation, the tumor cells begin to proliferate at 10 days after implantation, and the extracellular collagen fibers become disordered as the xenografts grow. In this study, nonlinear optical imaging was used to characterize the morphological details of fresh pancreatic tissues for the first time. It was demonstrated that it is possible to provide realtime histological evaluation of pancreatic cancer by the nonlinear optical methods, which present an opportunity for the characterization of the progress of spontaneous pancreatic cancer and further application in a non-invasive manner [277].

Dendritic cells

Pancreatic cancer is a malignant neoplasm with poor prognosis that might be associated with defective immune function. It was aimed to determine the influence on survival of circulating myeloid dendritic cells (c-m-DCs), circulating lymphoid DCs (c-I-DCs), and DCs within the tumor tissue in patients with pancreatic cancer. Between 2001 and 2006, of a total of 110 patients with ductal adenocarcinoma of the pancreas, 42 underwent pancreatectomy, and 68 had unresectable disease. Numbers of c-m-DCs and c-I-DCs were assessed by flow cytometry, and DCs in the tumor tissue by immunohistochemical staining with anti-fascin mAb. The percentage of the c-m-DCs subset in pancreatic cancer patients was significantly

lower than in healthy volunteers, and the similar finding was observed between patients who underwent surgical resection and non-resection. Patients with a high percentage of c-m-DCs or with many DCs accumulated in the cancer tissue survived longer than patients with a low percentage or low number in peripheral blood or the tumor, respectively. Moreover, there was a positive correlation between c-m-DCs within peripheral blood mononuclear cells and the number of DCs per field in the cancer tissue. It was concluded that preoperative c-m-DCs levels in the PBMC of patients with pancreatic cancer and DCs counts in the cancer tissue can be a prognostic factor after surgical resection. Modulating the distribution of DCs may be an effective therapy in pancreatic cancer patients with a dismal prognosis [278].

Symptoms and signs

Double duct sign

"Double-duct sign" (strictures in both common bile duct, CBD, and pancreatic duct, PD, with proximal dilation) on endoscopic retrograde cholangiopancreatography is considered suggestive of pancreatic malignancy. Dilation of CBD and PD is frequently noted on computed tomography/magnetic resonance imaging scans, sometimes found incidentally in patients without jaundice. The prevalence of malignancy in these patients is not established. In a retrospective analysis, consecutive patients who underwent endoscopic ultrasound (EUS) at a tertiary care hospital from 2002 to 2006 for suspected pancreatic malignancy and had double-duct sign on imaging were included. It was evaluated the prevalence of malignancy in patients with or without obstructive jaundice and performance characteristics of EUS-fine-needle aspiration (FNA) in diagnosing malignancy in this setting. A final diagnosis of pancreatic malignancy was made in 142 (86 %) of 166 patients with and 4 (6 %) of 68 without obstructive jaundice. The accuracy of EUS-FNA for diagnosing malignancy in patients with or without obstructive jaundice was 93 percent versus 99 percent. It was concluded that dilation of both PD and CBD on computed tomography/magnetic resonance imaging scans is suggestive of pancreatic malignancy. The prevalence of malignancy, however, is markedly lower in patients without obstructive jaundice but is clinically significant and merits further diagnostic evaluation. Endoscopic ultrasound-FNA is highly accurate for diagnosing malignancy in this setting [279].

Sarcoid-reaction

Sarcoidosis is a multisystem chronic granulomatous disease found predominantly in the lungs and lymph nodes. Its pathologic hallmark is the presence of systemic non-caseating granulomas; however, a variation of this disease known as "sarcoid-like reaction" has been described in patients with underlying cancer. Sarcoid-like reactions in patients with hepatopancreatobiliary (HPB) tumors are rare findings, with only 15 cases having been reported in the English language literature. These reactions can be found in local lymph nodes or in distant organs, and when present in patients with cancer, they can mimic metastatic disease on imaging, potentially resulting in incorrect cancer staging and management. It was described two cases of patients with HPB tumors who had distant organ disease on cross-sectional imaging suspicious for metastases, which on further workup were found to be sarcoid-like reactions. We also discuss malignancy-induced sarcoid-like reactions and provide a review of the literature of sarcoid-like reactions in the setting of HPB tumors [280].

Superficial venous thrombosis

In contrast to deep venous thrombosis and pulmonary embolism, superficial venous thrombosis has not been considered to be a marker of occult cancer. However, actual data

regarding the association are very limited. It was identified all patients in Denmark from 1994 to 2009 with a diagnosis of superficial venous thrombosis, deep venous thrombosis in the legs or pulmonary embolism using population-based health registries. The occurrence of cancer in the three venous thromboembolism cohorts was compared with the expected numbers of cases estimated using national incidence rates to compute standardised incidence ratios (SIRs). It was identified a total of 7663 patients with superficial venous thrombosis, 45,252 with deep venous thrombosis and 24,332 with pulmonary embolism. In the first year of follow-up, very similar proportions of patients in the three cohorts were diagnosed with cancer. The SIR was 2.46 (95 % confidence interval 2.10 to 2.86) for superficial venous thrombosis, 2.75 for deep venous thrombosis, and 3.27 for pulmonary embolism. After one year, the SIRs declined to 1.05, 1.11 and 1.15, respectively. For all three patient cohorts, particularly strong associations were found for cancers of the liver, lung, ovaries and pancreas as well as for non-Hodgkin's lymphoma. Thus, venous thrombosis, whenever it is seen in the lower limbs, is a preclinical marker of prevalent cancer, particularly during the first year after diagnosis [281].

Energy expenditure

Increased metabolic rate may play a role in cancer cachexia, especially when caloric intake is significantly reduced. It was studied the effect of tumor load on resting energy expenditure (REE) in patients with pancreatic cancer after normalizing for their daily caloric intake and body composition. The cross-sectional study included 45 patients with pancreatic cancer (15 postoperation) and 75 controls. Resting energy expenditure was measured by indirect calorimetry, body composition was measured by dual-energy x-ray absorptiometry, and energy intake was measured by 3-day food records. There were no differences between pancreatic cancer patients who underwent surgery and those who did not in any of the anthropometric or metabolic parameters tested. Body mass index, lean body mass, body fat percentage, and energy intake were significantly lower in patients with pancreatic cancer compared with healthy controls. Resting energy expenditure and the respiratory quotient were significantly lower in patients. There were no differences in REE between patients and controls when normalized by lean body mass. Respiratory quotients were significantly lower in patients who underwent surgery and in those who did not compared with controls. It was concluded that pancreatic cancer does not increase REE above the normal levels nor does tumor burden contribute to increasing REE. Decreased daily energy intake of our patients may have reduced measured REE [282].

Mestastases from pancreas

For the majority of patients, ductal adenocarcinoma of the pancreas remains a lethal disease. Currently, surgical extirpation for localized disease offers the only chance for longterm survival. It was reported a patient who underwent successful resection of isolated lung metastasis occurring 13 years after pancreatic cancer resection. A 59-year-old woman underwent distal pancreatectomy for pancreatic cancer 13 years previously, followed by adjuvant chemotherapy, and was followed-up at the outpatient clinic of a local hospital. From around June 2010, she noticed bloody sputum, so she visited a local hospital. Since her chest X-ray and CT revealed a 1.5 cm mass shadow in the segment 10 of her right lung and she was referred to the Respiratory Disease Center of our hospital. As a result of through examinations, she was strongly suspected of having lung metastasis of pancreatic cancer, and underwent partial pneumonectomy. Postoperative histopathological examination of the resected specimen was consistent with lung metastasis of pancreatic cancer. She is still alive and currently receives third line of chemotherapy. It was concluded that patients who have achieved long-term survival after pancreatic cancer resection and can tolerate surgery may benefit from resection of a lung metastasis of pancreatic cancer in terms of survival, if it controls the metastasis [283].

Evaluation with CT

The aim of one study was to explore the diagnostic performance of multidetector computed tomography (MDCT) in characterising pancreatic metastases. CT examinations of 17 patients affected by pancreatic metastases were retrospectively reviewed. The primary malignancy was renal cell carcinoma (RCC) in eight cases, uterine leiomyosarcoma in two, lung carcinoma in four and breast carcinoma in three. CT images were assessed for lesion number, size and morphology. Pancreatic lesions were solitary in seven cases and multiple in ten. Lesion size ranged between 8 and 40 mm. Metastases from RCC were hyperattenuating in the arterial phase, metastases from breast cancer and lung cancer were hypoattenuating and metastases from uterine leiomyosarcoma were inhomogeneous. Precise lesion characterisation was obtained by using CT examination in 12 cases. In the remaining five patients, all with solitary metastases from RCC, a precise diagnosis was not possible because the lesions could not be differentiated from a neuroendocrine tumour. MDCT allowed pancreatic metastases characterisation in 71 percent of cases. The lesions were the manifestation of widely disseminated neoplastic disease, with the exception of metastases from RCC, which were exclusively located in the pancreas [284].

Incidentalomas

Computed tomography angiography (CTA) is routinely used to diagnose thoracic aortic pathology and for surveillance after thoracic endovascular aortic repair. The purpose of our study was to assess the prevalence of unsuspected disease identified on CTA examination for thoracic aortic pathology and to determine potential clinical significance of these findings. A retrospective review of 242 patients (136 men and 106 women; mean age, 66 ± 14 years) referred for clinical evaluation of thoracic aortic pathology during a 12-year period was performed. CTA was acquired after obtaining full written informed consent and injecting nonionic contrast Omnipaque 350 intravenously. Subsequently, axial images were obtained from the thoracic inlet through the pubic symphysis. The prevalence of incidental findings was recorded. A finding was judged potentially significant if a therapeutic intervention or radiologic follow-up was deemed advisable on the basis of the CTA findings. Prevalence of incidental findings were noncalcified pulmonary lesions (subcentimeter nodule [12 %], nodule >1 cm [7 %], and pulmonary mass >3 cm [2 %]), calcified pulmonary nodules (15 %), simple liver cysts (13 %), contrast-enhancing liver lesion (3 %), renal mass (3 %), and pancreatic mass (2 %). Subsequent diagnostic tests were recommended for 63 findings in 55 (23 %) patients, which revealed 11 (5 %) patients had metastatic disease-six primary lung cancer, one metastatic lesion (mets) to the lung, one renal cell carcinoma with mets in the lung, one primary pancreatic adenocarcinoma with mets in the liver, one unknown primary with mets in the liver, and one other poorly differential metastatic carcinoma with lesions in the pancreas, adrenal glands, kidneys, and small bowel with unknown primary. Thus, CTA evaluation in patient with aortic pathology may reveal a high rate of malignant lesions. Attention to the incidental finding of suspicious lesion on computed tomographic scans in the chest and abdomen and appropriate follow-up by the requesting surgeon is important in patients undergoing surveillance for aortic pathologies [285].

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was recorded. A finding was judged potentially significant if a therapeutic intervention or radiologic follow-up was deemed advisable on the basis of the CTA findings. Prevalence of incidental findings were noncalcified pulmonary lesions (subcentimeter nodule, nodule >1 cm, and pulmonary mass >3 cm) calcified pulmonary nodules, simple liver cysts, contrastenhancing liver lesion, renal mass, and pancreatic mass (5, 2 %). Subsequent diagnostic tests were recommended for 63 findings in 55 patients, which revealed that 11 patients had metastatic disease-six primary lung cancer, one metastatic lesion (mets) to the lung, one renal cell carcinoma with mets in the lung, one primary pancreatic adenocarcinoma with mets in the liver, one unknown primary with mets in the liver, and one other poorly differential metastatic carcinoma with lesions in the pancreas, adrenal glands, kidneys, and small bowel with unknown primary. In conclusion, CTA evaluation in patient with aortic pathology may reveal a high rate of malignant lesions. Attention to the incidental finding of suspicious lesion on computed tomographic scans in the chest and abdomen and appropriate follow-up by the requesting surgeon is important in patients undergoing surveillance for aortic pathologies [286].

The purpose of one study was to review the CT findings and clinical outcome in patients with incidentally discovered solid pancreatic masses. Over an 8-year period, from 2001 to 2009, it was identified 24 patients with solid pancreatic masses incidentally detected by CT. There were 13 females and 11 males, with a mean age of 67 years. It was determined the indication for initial CT, analyzed the CT features, and ascertained the clinical follow-up in all the patients. All of the solid masses were malignant. There were 14 adenocarcinomas and 10 neuroendocrine tumors. The most common indications for the initial CT were surveillance of an extrapancreatic malignancy (n=10) and evaluation for hematuria (n=6). On the initial CT, 16 of the patients (67 %) had a clearly visible pancreatic mass. In eight patients isoattenuating masses were identified, only recognized by subtle signs including unexplained dilatation of the pancreatic duct (n=5) or minimal contour deformity or density of the pancreas (n=3). The mean survival time for the patients with adenocarcinoma was 22 months, and 42 months for the patients with neuroendocrine tumors. It was concluded that although uncommon, incidentally discovered solid pancreatic masses are malignant neoplasms, either ductal adenocarcinomas or neuroendocrine tumors. Unlike incidentally discovered small cystic lesions, solid pancreatic lesions are often biologically aggressive [287].

At screening

The risk of pancreatic cancer is increased in patients with a strong family history of pancreatic cancer or a predisposing germline mutation. Screening can detect curable, noninvasive pancreatic neoplasms, but the optimal imaging approach is not known. We determined the baseline prevalence and characteristics of pancreatic abnormalities using 3 imaging tests to screen asymptomatic, high-risk individuals (HRIs). It was screened 225 asymptomatic adult HRIs at 5 academic US medical centers once, using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). It was compared results in a blinded, independent fashion. Ninety-two of 216 HRIs (42 %) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n=5) by any of the imaging modalities. Fifty-one of the 84 HRIs with a cyst (61 %) had multiple lesions, typically small (mean 5.5 mm; range, 2-39 mm), in multiple locations. The prevalence of pancreatic lesions increased with age; they were detected in 14 percent of subjects younger than 50 years old, 34 percent of subjects 50-59 years old, and 53 percent of subjects 60-69 years old. CT, MRI, and EUS detected a pancreatic abnormality in 11, 33, and 43 percent of the HRIs, respectively. Among these abnormalities, proven or suspected neoplasms were identified in 85 HRIs (82 intraductal papillary mucinous neoplasms and 3 pancreatic endocrine tumors). Three of 5 HRIs who underwent pancreatic resection had high-grade dysplasia in less than 3 cm intraductal papillary mucinous neoplasms and in multiple intraepithelial neoplasias. It was concluded that screening of

asymptomatic HRIs frequently detects small pancreatic cysts, including curable, noninvasive high-grade neoplasms. EUS and MRI detect pancreatic lesions better than CT [288].

Diagnostics for pancreatic cancer

EUS

Prediction of vascular invasion

To evaluate the accuracy of endoscopic ultrasound (EUS) to determine vascular invasion in patients with pancreatic cancer data were obtained prospectively from patients with a pancreatic lesion who underwent EUS, computed tomographic (CT) imaging, and surgery from 2005 to 2010. Fifty patients were included with a mean ± SD age 61 ± 12 years; 27 (54 %) were women. The sensitivity, specificity, positive predictive value, and negative predictive value for EUS were the following: 61, 91, 79, and 80, respectively. The area under the curve for EUS and that for CT were 0.80 and 0.74, respectively. The positive predictive value for arterial invasion was 100 percent for EUS and 60 percent for CT. There were no complications associated with the EUS or the CT. Thus, endoscopic US is a very good option to detect vascular invasion in patients with pancreatic cancer and is especially sensitive for arterial invasion. When it is available, it was recommend that it be performed in addition to CT staging [289].

Trends in pancreatic pathology practice after implementation of EUS-FNA

Little has been reported on changes in pancreatic pathology practice after implementation of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). It was assessed the impact of EUS-FNA on cytologic diagnosis replacing histologic diagnosis for pancreatic disease and determined whether it fulfills Christensen criteria of a disruptive innovation effect. Pattern of utilization during 20 years, diagnostic categories, and diagnostic accuracy of pancreatic cytology were compared before and after implementation of EUS-FNA. The disruptive effect of cytology relevant to biopsy was assessed by comparing the utilization trends and the accuracy of diagnosis over time. The mean annual volume (+ standard deviation) of cytologic specimens increased from 24 + 11 to 231 + 10 after implementation of EUS-FNA, and that of histologic specimens increased from 97 ± 42 to 377 ± 14). The average percentage of annual cases managed by following cytology alone was 19 + 10 percent before versus 51 + 8 after implementation. The percentage managed by histology alone was 56 percent before versus 23 percent after implementation. Non-endoscopic ultrasound-guided fine-needle aspiration cytology decreased from 36 to 1 percent. Needle biopsies decreased from 7 to 1 percent, and other biopsy types from 29 to 9 percent. Unsatisfactory (7 % versus 1 %), atypical (16 % versus 4 %), and suspicious (16 % versus 3 %) diagnoses were significantly reduced. The accuracy of cytologic diagnosis significantly improved: the sensitivity and specificity for cancer diagnosis were 55 percent and 78 percentbefore versus 88 percent and 96 percent after implementation, respectively. It was concluded that endoscopic ultrasoundguided fine-needle aspiration improved the accuracy of cytologic diagnosis, reduced the number of indeterminate diagnoses, and replaced the need for tissue biopsy. Given its cost and simplicity as compared with tissue biopsy, this trend represents a disruptive innovation effect [290].

Contrast-enhanced EUS

Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS), a novel technology, visualizes parenchymal perfusion in the pancreas. One study prospectively evaluated how accurately CH-EUS characterizes pancreatic lesions and compared its diagnostic ability with that of contrast-enhanced multidetector-row computed tomography (MDCT) and endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA). A total of 277 consecutive

patients with pancreatic solid lesions that were detected by conventional EUS underwent CH-EUS for evaluation of vascularity. After infusing an ultrasound contrast, CH-EUS was performed by using an echoendoscope and a specific mode for contrast harmonic imaging. On the basis of the intensity of enhancement, the lesions were categorized into four patterns: nonenhancement, hypoenhancement, isoenhancement, and hyperenhancement. For comparison, all patients underwent MDCT. The ability of CH-EUS to differentiate ductal carcinomas from the other solid tumors, particularly small lesions (≤ 2 cm in diameter) was assessed, and compared with the differentiating abilities of MDCT and EUS-FNA. In terms of reading the CH-EUS images, the kappa-coefficient of the interobserver agreement test was 0.94. CH-EUS-depicted hypoenhancement diagnosed ductal carcinomas with a sensitivity and specificity of 95 percent (95 % confidence interval 93 to 97 %) and 89 percent (95 % confidence interval 83 to 93 %), respectively. For diagnosing small carcinomas by CH-EUS, the sensitivity and specificity were 91 percent and 94 percent, respectively. CH-EUSdepicted hypervascular enhancement diagnosed neuroendocrine tumors with a sensitivity and specificity of 79 percent and 99 percent respectively. Although CH-EUS and MDCT did not differ significantly in diagnostic ability with regard to all lesions, CH-EUS was superior to MDCT in diagnosing small (≤2 cm) carcinomas. In 12 neoplasms that MDCT failed to detect, 7 ductal carcinomas and 2 neuroendocrine tumors had hypoenhancement and hyperenhancement on CH-EUS, respectively. When CH-EUS was combined with EUS-FNA, the sensitivity of EUS-FNA increased from 92 to 100 percent. It was concluded that CH-EUS is useful for characterizing conventional EUS-detected solid pancreatic lesions. EUS equipped with contrast harmonic imaging may play an important role in the characterization of small tumors that other imaging methods fail to depict and may improve the diagnostic vield of EUS-FNA [291].

CT and MDCT

The purpose of one study was to evaluate CT perfusion of pancreatic carcinomas using the Patlak model for assessing perfusion, permeability, and blood volume. A total of 25 patients with pancreatic carcinoma were examined prospectively with a 64-slice computed tomography (CT) using a dynamic sequence after intravenous injection of 80-mL contrast material (370 mg/mL; flow rate, 5 mL/s). Eighty-kilovolt (peak) perfusion acquisitions were evaluated for estimating perfusion parameters for carcinoma and healthy tissue using a 2-compartment model (Patlak model). Twenty patients had hypodense tumors; in 5 patients, the tumor could not be delineated in contrast-enhanced CT. All carcinomas could be identified clearly in the color-coded perfusion maps. Perfusion, permeability, and blood volume values were significant lower in pancreatic carcinomas compared to healthy pancreatic tissue ($0.27 \pm 0.20 \text{ vs } 0.89 \pm 0.19 \text{ min}; 0.43 \pm 0.20 \text{ vs } 0.75 \pm 0.16 \times 0.5 \text{ min}; and 38.9 \pm 20.7 \text{ vs } 117.8 \pm 46.9 \text{ mL/100 mL}$. It was concluded that **c**omputed tomographic perfusion maps could be a helpful tool to delineate pancreatic carcinomas even if they are not visible in contrast-enhanced CT [292].

MDCT

CT perfusion has been proposed for pancreatic lesion characterization. However, scan and analysis protocols influence numerical data. To overcome this, the purpose of one study is to evaluate the use of time-density curves obtained from MDCT perfusion of the pancreas for the characterization of normal parenchyma, adenocarcinoma, chronic pancreatitis and endocrine tumors. Thirty-one patients with solid pancreatic lesions and 21 patients with renal cell carcinoma underwent 64-row MDCT perfusion of the pancreas after injection of 50 cc of a 370 mg l/mL solution at 5 cc/s. Sixty-three time-density curves were obtained from normal parenchyma (12) patients), adenocarcinoma (25), endocrine tumors (4) and atrophic parenchyma (13). Two readers independently categorized the 63 time-density curves into 4 different morphologies: normal wash-in and wash-out (A), low wash-in followed by plateau (B), low wash-in followed by faint wash-out (C) and high wash-in and wash-out (D).

Interobserver agreement was calculated with kappa statistics. Fisher test was used to calculate sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for each type of curve. Interobserver agreement was very good. Curve A had 94 percent sensitivity, 91 percent specificity, 81 percent PPV, and 98 percent NPV for "normal parenchyma". Curve B had 74 percent sensitivity, 94 percent specificity, 92 percent PPV, and 79 percent NPV in diagnosing "adenocarcinoma". Curve C had 45 percent sensitivity, 85 percent specificity, 38 percent PPV, and 88 percent NPV for "chronic pancreatitis". Curve D had 100 percent sensitivity, 98 percent specificity, 75 percent PPV, and 100 percent NPV for "endocrine tumor". It was concluded that the morphology of MDCT perfusion time-density curves appears to be useful in characterizing pancreatic lesions, and might help overcome the differences in scan and postprocessing techniques [293].

Precise assessment of retroperitoneal invasion is clinically important to allow the achievement of negative margin resections. The clinical records of 132 patients who underwent macroscopic curative pancreaticoduodenectomy for invasive ductal carcinoma of pancreas between 2004 and 2008 were retrospectively examined. The the clinicopathological factors, including retroperitoneal fat infiltration classified into four groups by multidetector-row computed tomography (MDCT), were analyzed. The relationship between the grade of retroperitoneal fat infiltration and surgical outcomes, as well as various histopathological factors, was also investigated. The 5 year survival rate was 55 percent for grade 0 infiltration (n=8), 39 percent for grade 1 (n=54), 16 percent for grade 2 (n=49), and 0 percent for grade 3 (n=21). There were significant differences in survival in each group. Extrapancreatic nerve invasion and the surgical margin status were significantly associated with retroperitoneal fat infiltration demonstrated on MDCT. According to the grading classification among the 43 patients with pathological portal vein invasion, the 5 year survival rate was 46 percent for patients with grade 1, which was significantly better survival that those with grade 2. It was concluded that the grading criteria for retroperitoneal fat infiltration may be useful as a predictor of survival after pancreaticoduodenectomy for pancreatic head carcinoma. Pancreaticoduodenectomy with portal vein resection could provide favorable survival in patients with grade 1 retroperitoneal fat infiltration, even if histopathological portal vein invasion is present [294].

CT angiography

To investigate the diagnostic performance of 64-section CTA in the detection of dorsal pancreatic artery before interventional therapy for patients with diabetes 42 consecutive patients with diabetes received an experimental treatment of autologous bone marrowderived stem cell transplantation by means of infusion into the dorsal pancreatic artery. All cases underwent abdominal CTA before angiography of pancreatic arteries in order to locate the origin and course of dorsal pancreatic artery. Angiography of coeliac artery, splenic artery, common hepatic artery and superior mesenteric artery were performed both in CTA and DSA. Superselective catheterization of dorsal pancreatic artery was carried out for the infusion of stem cell. Sensitivity, specificity and accuracy for the detection of dorsal pancreatic artery with CTA were calculated using DSA images as the reference standard. Thirty-five and thirty-six dorsal pancreatic arteries were detected by CTA and DSA respectively. Dorsal pancreatic artery was not visualized in either CTA or DSA in 5 patients. The sensitivity, specificity and accuracy for CTA were 94, 83 and 93 percent. It was concluded that 64-section CTA is accurate for the detection of dorsal pancreatic artery. It may be useful for the facilitation of superselective arterial infusion of stem cells to pancreas [295].

Dual-source dual-energy CT

To compare pancreatic virtual unenhanced (VUE) and true unenhanced (TUE) images and to calculate the potential dose reduction by omitting the conventional unenhanced scan. Fifty-one patients with known or suspected pancreatic masses underwent contrast-enhanced computed-tomography (CT) during unenhanced and portal venous phases acquired in

single-energy (SE) mode, and pancreatic parenchymal phase acquired in dual-energy (DE) mode. The image quality (IQ) and image noise (IN) of TUE and VUE images were evaluated. The effective dose of a combined DE/SE dual-phase protocol was compared with that of a theoretical standard SE triple-phase protocol. Mean TUE and VUE IQ were 1.5 ± 0.6 and 1.6 ± 0.6 , with no significant difference. Mean TUE and VUE IN were 12.3 ± 1.6 and 10.3 ± 1.5 HU, and resulted significantly different. Mean effective doses for a combined DE/SE dual-phase protocol were 8.9 ± 2.4 mSv (range 4.8 ± 16.2 mSv) and 12.1 ± 3.1 mSv (range 6.4 - 21.1 mSv). The calculated mean dose reduction achievable by omitting the unenhanced scan was 26.7 ± 9.7 percent (range 10 - 46.1). It was concluded that VUE images are feasible for pancreatic abdominal CT. A combined DE/SE dual-phase protocol permits a significant reduction in dose exposure to patients [296].

PET

The assessment of hepatobiliary and pancreatic tumors is commonly achieved by ultrasound, computed tomography (CT), and magnetic resonance. The 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) detects increased glucose metabolism associated with neoplastic lesions, provides high accuracy in most cancer imaging applications and is now widely used in clinical practice. However, PET is not always useful and accurate knowledge of appropriate indications is essential for a proper clinical management. ¹⁸F-FDG is transported into cells and phosphorylated by the enzyme hexokinase to ¹⁸F-FDG-6-phosphate, which cannot proceed down the glycolytic pathway and therefore is accumulated in the malignant tissue. PET allows accurate quantification of FDG uptake in tissue, and previous studies have demonstrated that standardized uptake values provide highly reproducible parameters of tumor glucose use [Weber et al. J Nucl Med 1999: 40: 1771-7]. The recent development and diffusion of hybrid PET-CT scanners allows functional and anatomic data to be obtained in a single examination, improving lesion localization and resulting in significant diagnostic improvement [Wahl, J Nucl Med 2004; 45: 82S-95S]. Moreover, CT can be performed diagnostically with the use of intravenous and oral contrast and simultaneous PET-contrast-enhanced CT scanning appears to be an efficient method in cancer evaluation. However, in most centers, a low-dose CT is routinely performed without contrast media infusion. Proper patient preparation, scanning protocol, combined assessment of PET and CT data, and the evaluation of conventional imaging findings are essential to define disease and to avoid diagnostic pitfalls. The role of PET and PET-CT in malignancies of the liver, biliary tract, and pancreas is here reviewed; normal patterns, representative cases, and common pitfalls are also presented [297].

Since 2006, the National Oncologic PET Registry has collected prospective data on ¹⁸F-FDG PET performed for cancer indications in Medicare beneficiaries under the coverage-withevidence-development (CED) policy of the Centers for Medicare & Medicaid Services. In April 2009, coverage for PET performed to inform the initial treatment strategy of most solid tumors was expanded by the Centers for Medicare & Medicaid Services, but they continued to require CED for subsequent treatment strategy evaluations for many cancers. For all years, it was assessed National Oncologic PET Registry data for bladder, kidney, pancreas, prostate, stomach, small cell lung, uterine, and all other cancers that required CED. It was compared clinical profiles and changes in intended management by interval (before or after April 2009, designated as the 2006 and 2009 cohorts) for PET scans performed for restaging or suspected recurrence (2006, n=30.911; 2009, n=54,747) or for chemotherapy monitoring (2006, n=10,234; 2009, n=15,611). There were slight differences between time periods but little difference by cancer type or patient age within a time period. For restaging or suspected recurrence, comparing the 2006 and 2009 cohorts, total change in intended management for all cancer types was about 33 percent in those younger than 65 y and about 35 percent in those older than 65 years (range by cancer type, 31 % to 41 %). The referring physician impression of disease extent (restaging) or prognosis (chemotherapy monitoring) after PET

was similar between cohorts. In the 2009 cohort, PET for chemotherapy monitoring was associated with a 25% increase in plans to continue therapy and a complementary decline in plans to adjust therapy. The greatest management impact of PET was during chemotherapy monitoring in the 2009 cohort, where a post-PET prognosis judged to be worse than before PET was associated with a plan to discontinue that therapy in 90 percent and to change to a different therapy in 65 percent. The data demonstrate a similar impact of PET on planned management of cancer patients before and after the 2009 expansion of coverage. These results strongly suggest it is unlikely that new useful information will be obtained by extending the coverage of certain cancer types and indications only under CED. Future research on advanced imaging in the management of patients with cancer should focus on optimal sequencing and frequency of PET and other imaging modalities [298].

Despite recent advances in clinical imaging modalities, differentiation of pancreatic masses remains difficult. Here, we tested the diagnostic accuracy of molecular-based imaging including 3'-deoxy-3'-18F-fluorothymidine (FLT) positron emission tomography (PET) and 18F-fluorodeoxyglucose (FDG) PET/CT in patients with suspected pancreatic masses scheduled to undergo surgery. A total of 46 patients with pancreatic tumours suspicious for malignancy and scheduled for resective surgery were recruited prospectively. In 41 patients, FLT PET and FDG PET/CT scans were performed. A diagnostic CT performed on a routine basis was available in 31 patients. FLT PET and FDG PET/CT emission images were acquired according to standard protocols. Tracer uptake in the tumour - FDG and FLT standardized uptake value (SUV) - was quantified by the region of interest (ROI) technique. For FDG PET/CT analysis, correct ROI placement was ensured via side-by-side reading of corresponding CT images. Of 41 patients, 33 had malignancy, whereas 8 patients had benign disease. Visual analysis of FDG and FLT PET resulted in sensitivity values of 91 percent (30/33) and 70 percent (23/33), respectively. Corresponding specificities were 50 percent (4/8) for FDG PET and 75 percent (6/8) for FLT PET. In the subgroup of patients with contrast-enhanced CT (n=31), sensitivities were 96 percent (PET/CT), 88 percent (CT alone), 92 percent (FDG PET) and 72 percent (FLT PET), respectively. Mean FLT uptake in all malignant tumours was 3.0 (range SUV_{max} 1.1-6.5; mean FDG SUV_{max} 7.9, range 3.3-17.8) For differentiation of pancreatic tumours, FDG PET and FDG PET/CT showed a higher sensitivity but lower specificity than FLT PET. Interestingly, visual analysis of FLT PET led to two false-positive findings by misinterpreting physiological bowel uptake as pathological FLT uptake in the pancreas. Due to the limited number of patients, the clinical value of adding FLT PET to the diagnostic workup of pancreatic tumours remains to be determined [299].

PET-CT

Fluorodeoxyglucose (FDG)-positron emission tomography/contrast-enhanced computed tomography (PET/CE-CT) involving whole-body scanning first by non-CE-CT and FDG-PET followed by CE-CT has been used for detailed examination of pancreatic lesions. It was evaluated PET/CE-CT images with regard to differential diagnosis, staging, treatment response, and postoperative recurrence in pancreatic cancer. Positron emission tomography/CE-CT was conducted in 108 patients with pancreatic cancer and in 41 patients with other pancreatic tumor diseases. The maximum standardized uptake value (SUVmax) overlapped in benign and malignant cases, suggesting that differential diagnosis of pancreatic tumors based on the SUVmax is difficult. In the evaluation of staging in 31 resectable pancreatic cancers by PET/CE-CT, the diagnostic accuracy rate was more than 80 percent for most factors concerning local invasion and 94 percent for distant metastasis but only 42 percent for lymph node metastasis. Significant positive correlations were found between the SUVmax and tumor size/markers, suggesting that SUVmax may be a useful indicator for the treatment response. Regarding the diagnosis of the postoperative recurrence, PET/CE-CT correctly detected local recurrence in all the 11 cases of recurrence, whereas abdominal CE-CT detected only 7 of 11 cases, suggesting that PET/CE-CT is

superior in this context. Positron emission tomography/CE-CT is useful for the clinical management of pancreatic cancer [300].

MRI

To compare the apparent diffusion coefficients (ADCs) of pancreatic adenocarcinomas that appears hyperintense with clearly defined borders (clear hyperintense) with those that do not show clear hyperintense borders on diffusion-weighted magnetic resonance (MR) images. Eighty patients with histologically confirmed pancreatic adenocarcinoma (mean tumor size, 32 mm) underwent fat-suppressed single-shot echo-planar 3.0-T diffusion-weighted MR imaging with diffusion gradients ($b = 1000 \text{ sec/mm}^2$). ADC values of the pancreatic adenocarcinomas (n=80) and proximal (n=51) and distal (n=70) pancreas were compared by using the Friedman test, followed by the Wilcoxon signed-rank test, and the difference in serum amylase levels between pancreatic adenocarcinomas with and without clear hyperintensity was evaluated by using the x^2 test. In 38 of 80 patients, pancreatic adenocarcinomas showed clear hyperintensity relative to the surrounding pancreas; 26 were hyperintense with unclear distal borders; 12, isointense; and four, hypointense. In all patients, the mean ADC (± standard deviation) of the tumors was significantly lower than those of the proximal pancreas and the distal pancreatic parenchyma. No significant difference in ADC was seen between the pancreatic adenocarcinomas without clear hyperintensity and the distal pancreas. The frequency of serum amylase levels greater than 120 U/L (2.00 microkat/L) was significantly higher than in those with clear hyperintense pancreatic adenocarcinomas Diffusion-weighted MR imaging was not useful for delineating 47% of pancreatic adenocarcinomas, because of hyperintensity of the pancreatic parenchyma distal to the cancer [301].

Tumor circulation according to MRI

To investigate the microcirculation in pancreatic cancer by pharmacokinetic analysis of multiple breath-hold dynamic contrast-enhanced magnetic resonance imaging at 3.0T multiple breath-hold dynamic contrast-enhanced magnetic resonance imaging was performed in 40 healthy volunteers and 40 patients with pancreatic cancer proven by histopathology using an axial three-dimensions fat-saturated T1-weighted spoiled-gradient echo sequence at 3.0T. A two compartment model with T1 correction was used to quantify the transfer constant, the rate constant of backflux from the extravascular extracellular space to the plasma and the extravascular extracellular space fractional volume in pancreatic cancer, obstructive pancreatitis distal to the malignant tumor, adjacent pancreatic tissue proximal to the tumor and normal pancreas. All parameters were statistically analyzed. Statistical differences were noticed in both the transfer constant and the rate constant of backflux among different tissues. Both the transfer constant and the rate constant of backflux in pancreatic cancer were statistically lower than those in normal pancreas and adjacent pancreatic tissue. Both the transfer constant and the rate constant of backflux in obstructive pancreatitis were statistically lower than those in normal pancreas and adjacent pancreatic tissue. The extravascular extracellular space fractional volume in pancreatic cancer was statistically lager than that in normal pancreas. Multiple breath-hold dynamic contrastenhanced magnetic resonance imaging offers a useful technique to evaluate the microenvironment in pancreatic cancer at 3.0T. Compared to normal pancreas, pancreatic cancer has lower transfer constant, rate constant of backflux and larger extravascular extracellular space fractional volume [302].

Nuclear magnetic resonance spectroscopy

The aims of one study were to determine nuclear magnetic resonance spectroscopic characteristics and metabolite profiles of serum samples from patients with pancreatic cancer compared with noncancerous control samples, and to ascertain if the accuracy of metabolite

identification by 1D spectra can be improved upon by confirmation of spin-system assignment using more sophisticated experiments. Nuclear magnetic resonance spectra, including 1D, total correlation spectroscopy, and heteronuclear multiple/single quantum coherence, were obtained from serum samples from patients with pancreatic cancer and control subjects and used to determine serum levels of a range of metabolites. The data show that total choline, taurine, and glucose plus triglycerides are significantly higher in cancer versus control samples. Also detected were species that could not be individually identified and that were designated UCM (unresolved complex matter). Levels of UCM are significantly higher in subjects with cancer, being almost double those of control samples. It was concluded that although metabolites such as lactate, taurine, glucose, choline, and triglycerides can be determined from 1D spectra, accuracy is improved by confirmation of spin-system assignment with total correlation spectroscopy and heteronuclear multiple/single quantum coherence spectral analysis. In addition, we introduce a new metric, UCM, which is at higher concentrations in cancer compared with control samples [303].

Cytology

To elucidate the diagnostic efficacy of the cell block method by comparing it with that of conventional smear cytology for pancreatic juice obtained by endoscopic retrograde cholangiopancreatography (ERCP) in a randomized controlled trial fashion a total of 170 patients with pancreatic lesions suspicious of being malignant who underwent pancreatic juice collection without giving secretin under ERCP were enrolled in a study. After sampling, the pancreatic juice was randomized to the cell block method (n=85) or to smear cytology (n=85). Cell block sections were subjected to hematoxylin-eosin, periodic acid Schiff-Alcian blue, and immunohistochemical stains. Both Papanicolaou stain and Giemsa stain were used for smear cytology. The final diagnosis was malignancy in 54 patients: pancreatic cancer, 45; intraductal papillary-mucinous carcinoma,6; and endocrine tumor, 3. The number of patients with a cytological borderline malignancy in the cell block group (4 %) was significantly smaller than that in the smear group (27 %). The diagnostic accuracy of the cell block method and that of smear cytology were 77 percent (65/85) and 74 percent (63/85), respectively, and their respective sensitivities were 50 percent (14/28) and 39 percent (10/26). The sensitivity of the cell block method (89 %) was better than that of smear cytology (43 %) for invasive ductal carcinoma in the pancreas head. The cell block method using immunostaining for pancreatic juice cytology showed a much lower rate of equivocal borderline malignancy and a tendency for a higher diagnostic yield compared with smear cytology. Its diagnostic sensitivity, however, was not satisfactory except for pancreatic-head cancer [304].

EUS-guided FNA

To determine the yield of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in combination with immunostains in diagnosing unusual solid pancreatic masses in comparison with pancreatic adenocarcinoma (ACP) all EUS-FNA of solid pancreatic masses performed with a 22-gauge needle were included. Data on clinical presentations, mass characteristics, presence of pancreatitis, yield of tissue, and final diagnosis were compared between the two groups. On site cytopathology was provided and additional passes were requested to perform immunostains. Two hundred and twenty-nine cases with either adenocarcinoma or unusual solid pancreatic masses were included. The median age of the cohort was 65 years. ACP (210/229, 92 %) accounted for the majority of the cases. The unusual solid pancreatic masses included neuroendocrine (NET) masses (n=13), metastatic renal carcinoma (n=3), metastatic melanoma (n=1), lymphoma (n=1), and malignant fibrous histiocytoma (n=1). Subjects with ACP were significantly more likely to present with loss of weight or obstructive jaundice. Subjects with ACP were more likely to have suspicious/atypical FNA biopsy results as compared with unusual solid pancreatic masses

(10 % vs 0 %). The sensitivity of EUS-FNA with immunostains was 93 percent in ACP as compared with 100 percent in unusual solid pancreatic masses. Diagnostic accuracy was higher in unusual solid pancreatic masses as compared with ACP (100 % vs 93 %). It was concluded that EUS-FNA using a 22-gauge needle with immunostains has excellent diagnostic yield in patients with USPMs, which is comparable if not superior to the yield in pancreatic adenocarcinoma [305].

Preoperative diagnosis of solid pancreatic lesions remains challenging despite advancement in imaging technologies. EUS has the benefit of being a minimally invasive, well-tolerated procedure, although results are operator-dependent. The addition of FNA (EUS-guided FNA) provides samples for cytopathologic analysis, a major advantage over other imaging techniques. It was presented a meta-analysis of published studies assessing the diagnostic capability of EUS-FNA. Relevant studies were identified via MEDLINE and were included if they used a reference standard of definitive surgical histology or clinical follow-up of at least 6 months. Data from selected studies were analyzed by using test accuracy meta-analysis software, providing a pooled value for sensitivity, specificity, diagnostic odds ratio, and summary receiver operating characteristic curve. Cytology results were classified as inadequate, benign, atypical, suspicious, or malignant. Predefined subgroup analysis was performed. Thirty-three studies published between 1997 and 2009 were included, with a total number of 4984 patients. The pooled sensitivity for malignant cytology was 85 percent (95 % confidence interval 84 to 86 %), and pooled specificity was 98 percent (95 % confidence interval 0.97 to 0.99). If atypical and suspicious cytology results were included to determine true neoplasms, the sensitivity increased to 91 percent, however, the specificity was reduced to 94 percent. The diagnostic accuracy of EUS-FNA was enhanced in prospective, multicenter studies. This meta-analysis demonstrates that EUS-FNA is a highly accurate diagnostic test for solid neoplasms of the pancreas and should be considered when algorithms for investigating solid pancreatic lesions are being planned [306].

Over the past two decades, endoscopic ultrasound-guided fine-needle aspiration has evolved to become an indispensable tool for tissue acquisition in patients with gastrointestinal tumors. The technique is useful for biopsy of mucosal and submucosal lesions in which prior endoscopic biopsies have been nondiagnostic; to sample peri-intestinal structures such as lymph nodes; and to sample masses in the pancreas, liver, adrenal glands, gallbladder, and bile duct. Also, with the advent of neoadjuvant therapies for diseases such as pancreatic cancer, most patients require a tissue diagnosis before initiating treatment. One review provided a perspective on technical issues that are key for best practices in endoscopic ultrasound-guided fine-needle aspiration [307].

Brush cytology

The specificity of brush cytology for detection of malignant pancreatobiliary strictures is high, but its sensitivity is moderate. Fluorescence in situ hybridization (FISH) can be used to detect chromosomal aneuploidy in biliary brushing specimens, and, according to some reports, it may improve the sensitivity of routine cytology. In a prospective study performed between 2008 and 2010 a study involved 81 patients with bile duct or pancreatic duct strictures. Brush cytology obtained during ERCP from pancreatic duct or bile duct strictures and analysis of smears by routine cytology and FISH. The sensitivity of routine cytology was 35 percent, and specificity was 100 percent. When atypia was identified as positive, the resultant sensitivity was 54 percent, and specificity was 100 percent. When either routine cytology was positive or atypia was observed or when the FISH result was positive, sensitivity was the highest (72 %), and it was statistically significant in comparison with both routine cytology with atypia and FISH, but specificity was lower than that of routine cytology (89 % vs 100 %). It was concluded that FISH improved the sensitivity of routine cytology. Pancreatic duct brushings were a reliable

material for detection of chromosomal abnormalities by FISH. The best diagnostic result was achieved by combining routine cytology with FISH [308].

Cytodiagnostic endoscopic nasopancreatic drainage

It was examined the results of pancreatic juice cytodiagnosis using the method of endoscopic nasopancreatic drainage (ENPD) to identify pancreatic carcinoma in situ and compared the images and pathologic diagnosis of pancreatic carcinoma in situ as well as clinicopathologic characteristics. In patients who underwent endoscopic retrograde cholangiopancreatography and had ENPD place, only patients presenting with focal stenosis and distal dilatation of the main pancreatic duct were included in the ENPD placement group. Endoscopic nasopancreatic drainage was conducted 27 times in 20 patients in the ENPD placement group. In an average session, cytodiagnosis of the pancreatic juice was conducted 5 times (range, 2-11 times). Results of cytodiagnosis were positive in 15 of 20 patients. Results of ENPD cytodiagnosis and diagnosis of pancreatic cancer showed sensitivity of 100 percent, specificity of 83 percent, and accuracy of 95 percent. Seven of 15 patients were diagnosed with carcinoma in situ. In these 7 patients, tumor markers (carcinoembryonic antigen, CA-19-9) were within reference limits, and the tumors were not visible on imaging tests. Pathologic histology revealed a propensity for the cancer to proliferate around the stenosis of the pancreatic duct. Cytodiagnosis of pancreatic juice using ENPD multiple times proved to be useful in the diagnosis of pancreatic carcinoma in situ [309].

CEA

The objective of one study was to assess the efficacy of carcinoembryonic antigen (CEA) for differentiating and diagnosis of pancreatic and liver diseases. A hospital based retrospective study was carried out using data retrieved from the register maintained between January and October, 2011. Estimation of CEA was performed by ELISA reader for all cases. Of the 771 subjects, 208 (27 %), 60 (8 %), 240 (31 %), 54 (7 %) , 75 (10 %), 59 (8 %), 75 (10 %) cases were of active chronic hepatitis , cryptogenic cirrhosis, alcoholic cirrhosis, primary biliary cirrhosis, hepatoma, acute or chronic pancreatitis, carcinoma of pancreas respectively. There were no cases having more than 20 ng/mL of CEA in acute or chronic pancreatitis. In cases of pancreatic cancer, maximum number of cases (35) were having CEA >20 ng/mL (47 %). It was concluded that high levels of CEA are associated with advanced stage of disease. CEA can thus provide an important improvement in the diagnosis by differentiating pancreatic cancer especially from chronic pancreatitis when there is a high suspicion of malignancy [310].

Radiofrequency spectral parameters

Spectral analysis of the radiofrequency (RF) signals that underlie grayscale EUS images has been used to provide quantitative, objective information about tissue histology. The purpose of one study was to validate RF spectral analysis as a method to distinguish between chronic pancreatitis (CP) and pancreatic cancer (PC). A prospective study of eligible patients was conducted to analyze the RF data obtained by using electronic array echoendoscopes. Pancreatic images were obtained by using electronic array echoendoscopes from 41 patients in a prospective study, including 15 patients with PC, 15 with CP, and 11 with a normal pancreas. Midband fit, slope, intercept, correlation coefficient, and root mean square deviation from a linear regression of the calibrated power spectra were determined and compared among the groups. Statistical analysis showed that significant differences were observable between groups for mean midband fit, intercept, and root mean square deviation. Discriminant analysis of these parameters was then performed to classify the data. For CP (n=15) versus PC (m=15), the same parameters provided 83 percent accuracy and an area under the curve of 0.83. The study showed that mean spectral parameters of the

backscattered signals obtained by using electronic array echoendoscopes can provide a noninvasive method to quantitatively discriminate between xhronic pancreatitis and pancreatic cancer [311].

Screening for pancreatic cancer

Pancreatic cancer (PC) is a highly lethal disease. Despite advances regarding the safety and long-term results of pancreatectomies, early diagnosis remains the only hope for cure. This necessitates the implementation of an intensive screening program (based mainly on modern imaging), which – given the incidence of PC – is not cost effective for the general population. However, this screening program is recommended for individuals at high-risk for PC development. Indications for screening include the following three clinical settings: hereditary cancer predisposition syndromes associated with PC, hereditary pancreatitis and familial pancreatic cancer syndrome. The aim of this strategy is to identify pre-invasive (precursor) lesions, which are curable. Surgery is recommended in the presence of recognizable lesion on imaging lesions. Partial (anatomic) pancreatectomy – depending on the location of the suspicious lesion – is the most widely accepted type of surgical intervention in this setting; occasionally, however, total pancreatectomy may be required, in carefully selected patients. Despite that experience still remains limited, there is evidence that this aggressive strategy allows early detection of neoplastic lesions, thereby improving the effectiveness of surgery and prognosis [312].

Approximately 10 percent of pancreatic cancer is hereditary, but a person's risk of developing this cancer increases two- to three-fold if a first-degree relative (parent, sibling or child) has pancreatic cancer. Presently, the United States Preventive Services Task Force (USPSTF) recommends against routine screening for PC in the general population because of the low prevalence of this malignancy, the limited accuracy and invasiveness of the currently available tests, and the poor outcomes of treatment. However, screening at-risk individuals is receiving increasing support with a recommended threshold to offer screening to those who carry a ≥10-fold increased risk. Recent advances in screening technology via serum or stool tests or endoscopic ultrasound (EUS) hold promise for detecting early-stage PC. A blood or stool test for early detection of PC would be preferable to EUS because of lower invasiveness and cost, however, biomarkers for PC are elusive and the efficacy of emerging potential serum or stool panels remains unknown with regard to early detection. The ability of EUS to assist in diagnosing pancreatic malignancies has also been demonstrated. However, concerns with EUS relate to its invasive nature, cost, accuracy and availability. At the present time, blood and stool tests and EUS remain areas of research as potential screening tools for PC. Studies are underway to provide a stronger rationale for their use among appropriate groups at particular risk for developing PC, including a recent report addressing the psychological impact of PC surveillance among at-risk participants in a Dutch PC surveillance study. This study, which included only at-risk individuals who already agreed to surveillance, demonstrated that surveillance was not associated with increased cancer worry or elevated anxiety or depression levels. Understanding the perceptions of atrisk, unaffected PC family members who are not enrolled in surveillance regarding future screening options is important and comparing their perceptions to individuals not at particular risk of PC would fill an existing gap in the literature. Individuals with a family history of cancer may overestimate their personal cancer risk and report increased cancer-related worry or concern; these factors may in turn positively or negatively influence attitudes and behaviors toward screening among this higher-risk group. Receptivity toward potential future screening options for pancreatic cancer among those at significant risk is an important, yet understudied area. The purpose of one study was to assess attitudes of at-risk family members with two or more relatives affected with pancreas cancer toward PC risk and future screening options. At-risk family members and primary care controls were surveyed

regarding perceived PC risk, PC worry/concern, attitude toward cancer screening, screening test accuracy, and intentions regarding PC screening via blood testing or more invasive endoscopic ultrasound (EUS). PC family members reported significantly greater perceived risk of PC than controls (54 % vs 6%, respectively). PC family members also reported higher levels of PC worry/concern than controls, although 19 percent of PC family members indicated they were "not at all concerned" about getting PC. PC family members indicated greater acceptance of a false-negative result on a PC screening test relative to controls (12 % vs 8 %). Both groups reported high (>89 %) receptivity to the potential PC screening options presented, though receptivity was greater among PC family members as compared to controls for EUS. In multivariable analyses, degree of PC concern was associated with intention to screen for PC by blood test and EUS, while perceived PC risk was associated with likelihood of undergoing EUS only. Overall, receptivity toward screening was higher among PC family members relative to controls; of the potential screening options studied, receptivity was greater for the less invasive method (blood test vs EUS). Previous studies including highly-selected, at-risk individuals have reported actual uptake of PC screening ranging between 61 percent (for EUS) and 67 percent (for MRI), which reflects variation in individual preferences and provides evidence that uptake cannot always be assumed. Moreover, this study established that individuals who have family members with PC may exhibit greater worry and concern about PC, perceive greater PC risk for themselves and that these psychological responses are independent, positive predictors of intention to undergo screening for PC via blood test (worry/concern) and EUS (worry/concern and perceived risk) were such screening tests to become available in the future. Willingness to undergo invasive procedures would be less likely for an average risk group of individuals, while those with heightened risk perception, greater perceived susceptibility or vulnerability and increased awareness of the severity of the target disease, would express greater likelihood of undergoing even an invasive screening test such as EUS. This point underscores the importance of understanding the nature of risk perception and concern in cancer screening and the importance of allowing such perceptions to appropriately drive screening behavior. It also underscores the importance of appropriate education on risk to family members. In this study, individuals who perceived themselves as likely to get PC in their lifetime were over three times as likely as those who did not hold this perception to be willing to undergo EUS screening, irrespective of group status. Thus, there is a great need to measure and understand the complexities of these constructs more fully in future research on PC. Patient education regarding PC risk and recommendations for surveillance among those at high risk is needed. Sensitivity and specificity of screening tests are sophisticated, yet critical concepts for patients to understand prior to undergoing a screening test. The difference observed in the study between PC family members and controls with regard to acceptance of false negatives is a novel finding warranting further study. Greater acceptance of personal false negative test results among PC family members may reflect an experiential bias (relative to controls) that treatment is only rarely successful in changing the course of the disease, thus, "missing" the diagnosis can be viewed with greater acceptance. This interpretation, if valid, may reflect both cognitive (actual knowledge-based) and affective (emotional) responses resulting from experience with the course of PC in their family member. This same logic would support the trend-level findings observed regarding greater global acceptance of missing a diagnosis of PC among PC family members as compared to controls [313].

High-risk individuals

The risk of pancreatic cancer is increased in patients with a strong family history of pancreatic cancer or a predisposing germline mutation. Screening can detect curable, noninvasive pancreatic neoplasms, but the optimal imaging approach is not known. We determined the baseline prevalence and characteristics of pancreatic abnormalities using 3 imaging tests to screen asymptomatic, high-risk individuals (HRIs). It was screened 225 asymptomatic adult HRIs at 5 academic US medical centers once, using computed

tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We compared results in a blinded, independent fashion. Ninety-two of 216 HRIs (42 %) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n=5) by any of the imaging modalities. Fifty-one of the 84 HRIs with a cyst (61 %) had multiple lesions, typically small (mean, 0.6 cm; range, 2-39 mm), in multiple locations. The prevalence of pancreatic lesions increased with age; they were detected in 14 percent of subjects younger than 50 years old, 34 percent of subjects 50-59 years old, and 53 percent of subjects 60-69 years old. CT, MRI, and EUS detected a pancreatic abnormality in 11 percent, 33 percent, and 43 percent of the HRIs, respectively. Among these abnormalities, proven or suspected neoplasms were identified in 85 HRIs (82 intraductal papillary mucinous neoplasms and 3 pancreatic endocrine tumors). Three of 5 HRIs who underwent pancreatic resection had high-grade dysplasia in less than 3 cm intraductal papillary mucinous neoplasms and in multiple intraepithelial neoplasias. It was concluded that screening of asymptomatic HRIs frequently detects small pancreatic cysts, including curable, noninvasive high-grade neoplasms. EUS and MRI detect pancreatic lesions better than CT [314].

Preoperative management

Pancreatic cancer is one of the least common tumors, nevertheless it is one of the most lethal. This lethality is mainly due to the fact that the vast majority of patients are diagnosed in an advanced stage. The objective of this work was to investigate how different covariates affect the transition to death after a first admission due to pancreatic cancer. It was analyzed the impact of different factors on health related transitions after a first hospital admission related to pancreatic cancer based on a multi state model. Transitions of interest include the transition to death (i.e. survival time), but also the time between a first admission and discharge or between discharge and readmission. It was consider comorbidities, the type of admission, and especially the performance of pancreas surgery as covariates with a potential effect on the transition intensities. It was concluded that a multi state model allows for a very detailed analysis since all covariate effects may change depending on the current state of the patient [315].

Anesthesiology

Excess use of intravenous fluid can increase post-operative complications. It was examined the influence of intra-operative crystalloid (IOC) administration on complications following pancreaticodudenectomy (PD) for pancreatic adenocarcinoma. It was categorized 188 patients who underwent PD for adenocarcinoma (1990-2009) into two groups: group I received <6,000 ml and group II received \geq 6,000 ml IOC. Differences between groups in length of stay, overall morbidity, and 30-day mortality were evaluated. There were 86 patients in group I and 102 in group II. Group I patients were older and with higher percentage of women, but similar in regards to performance status, ASA score, underlying comorbidities, and administration of neo-adjuvant treatment. Group II patients had longer operations, increased blood loss, and higher rates of intra-operative blood transfusions. There were two post-operative deaths, both in the group II. Post-operative overall morbidity was 46 percent, without differences between the two groups (44 % vs 47 %). Likewise, length of post-operative stay was similar in both groups (14 days vs 15 days). The volume of IOC increased with duration of surgery, intra-operative blood losses, and intra-operative blood transfusion, but did not correlate with post-operative morbidity [316].

Surgical overview

Pancreatic cancer patients have an extremely poor survival prognosis, and surgical resection remains the only curative treatment. Greater experience in pancreatic surgery and developments in surgical techniques have reduced surgical mortality and morbidity rates. It has been suggested that experienced pancreaticoduodenectomy centers should have mortality rates of less than 5 percent and major complication rates of less than 40 percent. Surgical resection followed by combined adjuvant therapy is currently the standard treatment for resectable pancreas cancer. Patients with borderline or marginal resectable tumors are beginning to have favorable outcomes following neoadiuvant chemotherapy or chemoradiation. A number of prospective randomized trials have concluded that "extended" pancreaticoduodenectomy for pancreatic head cancer, involving radical dissection of lymph nodes and peripancreatic soft tissue, does not appear to provide any survival benefits compared with "standard" pancreaticoduodenectomy. Conversely, extensive surgery for pancreatic tail or body cancer (i.e., radical antegrade modular pancreatosplenectomy) can result in favorable R0 resection rates and survival outcomes. However, more prospective randomized trial data are required before these conclusions can be considered established. Laparoscopic approaches are being increasingly used in the field of pancreatic tumor surgery. Moreover, robotic-assisted laparoscopic surgery has also been tried in some expert centers. Again, at present a lack of outcome data prevent any definitive conclusion at this stage on the usefulness of those approaches compared to standard open approaches. Finally, a major problem hindering efforts to identify optimal surgical treatment modalities for pancreas cancer is the lack of a clear definition and standardization of surgical procedures and pathologic descriptions [317].

To describe the management and outcomes of a population-based cohort of patients with pancreatic cancer in Victoria, Australia a retrospective study based on questionnaires completed from medical histories of patients diagnosed with pancreatic cancer during 2002-2003 who were identified from a cancer registry and followed up for 6 years was performed. Of 1044 patients with pancreatic cancer identified, 927 were eligible for the study, and questionnaires were completed for 830 (response rate, 90 %); 67 patients with ampulla of Vater and neuroendocrine tumours were excluded. Of the 763 remaining patients (median age, 72 years), notification of death was available for 747 (98 %). Most patients (n=548) had tumours in the head and neck of the pancreas. Resection was performed in a total of 87 patients (11 %). Patients managed with Whipple resection (n=75) had a 30-day mortality rate of 5.3 percent and median survival of 16 months. A relatively large number of surgeons (n=31) each performed a modest number of Whipple resections during the study period. Jaundice was palliated with biliary stents (n=240) and bypass surgery (n=99). Survival was shortest in those treated with best supportive care (median, 2 months for those with head and neck of pancreas tumours, and 3 months for body and tail of pancreas tumours). Of the 20 patients who survived to 5 years, 10 did not have histological confirmation of carcinoma and were presumably false-positive diagnoses, and three of the 10 patients who did have positive histological results had experienced recurrent disease by 6-year follow-up. Most outcomes in Victoria compared favourably with other studies. Prognosis for patients with carcinoma of the pancreas is grim, with few long-term survivors. Six-year survival appears to be a better proxy for cure than 5-year survival [318].

Pancreatic cancer patients have an extremely poor survival prognosis, and surgical resection remains the only curative treatment. Greater experience in pancreatic surgery and developments in surgical techniques have reduced surgical mortality and morbidity rates. It has been suggested that experienced pancreaticoduodenectomy centers should have mortality rates of less than 5 percent and major complication rates of less than 40 percent. Surgical resection followed by combined adjuvant therapy is currently the standard treatment for resectable pancreas cancer. Patients with borderline or marginal resectable tumors are

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Minimal invasive pancreatic surgery (laparoscopy)

Laparoscopic pancreas surgery has undergone rapid development over the past decade. Although acceptability among traditional surgeons has been low, emerging specialty centers are reporting excellent outcomes for advanced and complex operations, such as pancreaticoduodenectomy. A note of caution is necessary: These outstanding results are from skilled surgeons, many of whom are pioneers in the field, who have overcome the learning curve over many years of innovation. As the procedures gain wider practice, outcomes need to be carefully watched because many of these procedures are extremely demanding technically. Although many have suggested that controlled, randomized studies comparing laparoscopic pancreatic resections with open resections are necessary to establish the efficacy of laparoscopic procedure, the cumulative data on the safety and efficacy of the laparoscopic procedure argues against such an approach. The logistic difficulties of conducting such studies will be considerable given patient preferences, the need for multicenter studies, and the rapid adoption of the laparoscopic procedure among experienced pancreatic surgeons. A more reasonable approach to truly evaluate the safety of these procedures is the establishment of a national registry that can measure progress of the field and record outcomes in the wider, nonspecialty community. Hepatobiliary training programs should also establish a minimal standard of training for many of the advanced procedures, such as the pancreaticoduodenectomy, so that the benefit of laparoscopic surgery can be made available outside of just a few specialty centers [320].

Organisation of surgery

Low-volume versus high-volume hospitals

Previous literature has consistently shown worse operative outcomes at low-volume hospitals (LVH) after complex cancer surgery. Whether patient-related factors impact this association remains unknown. It was hypothesized that patient-related factors contribute to receipt of complex cancer surgery at LVH. Using the 2003-2008 National Inpatient Sample, it was identified 59,841 patients who underwent cancer operations for lung, esophagus, and pancreas tumors. Logistic regression models were used to examine the impact of sociodemographic factors on receipt of complex cancer surgery at LVH. Overall, 38 percent received their cancer surgery at LVH. A higher proportion of esophagectomies were performed at LVH (70 %), followed by pancreatectomy (38 %) and lung resection (34 %). Patients who were non-white, with non-private insurance, and had more comorbidities were all more likely to receive their cancer surgery at LVH. Multivariate analyses continued to

demonstrate that non-white race, insurance status, increased comorbidities, region, and nonelective admission predicted receipt of cancer surgery at LVH across all 3 procedures. In this large national study, non-white race and increased comorbidities contributed to receipt of cancer surgery at LVH. Patient selection and access to high-volume hospitals are likely reasons worthy of additional investigation. This study provides additional insight into the volume-outcomes relationship. Given the demonstrated outcomes disparity between high-volume hospitals and LVH, future policy and research should encourage mechanisms for referral of patients with cancer to high-volume hospitals for their surgical care [321].

The Netherlands

The impact of nationwide centralization of pancreaticoduodenectomy (PD) on mortality is largely unknown. The aim of one study was to analyse changes in hospital volumes and inhospital mortality after PD in the Netherlands between 2004 and 2009. Nationwide data on International Classification of Diseases, ninth revision (ICD-9) code 5-526 (PD, including Whipple), patient age, sex and mortality were retrieved from the independent nationwide KiwaPrismant registry. Based on established cut-off points of annually performed PDs, hospitals were categorized as very low (fewer than 5), low (5-10), medium (11-19) or high (at least 20) volume. A subgroup analysis based on a cut-off age of 70 years was also performed. Some 2155 PDs were included. The number of hospitals performing PD decreased from 48 in 2004 to 30 in 2009. In these specific years, the proportion of patients undergoing PD in a medium- or high-volume centre increased from 53 to 91 percent. Nationwide mortality rates after PD significantly decreased from 9.8 to 5.1 percent. The mortality rate during the 6-year period was 14.7, 9.8, 6.3 and 3.3 percent in very low-, low-, medium- and high-volume hospitals respectively. The difference in mortality between medium- and high-volume centres was statistically significant. The volume-outcome relationship was not influenced by age. The mortality rate after PD in patients aged at least 70 years was 10.4 percent compared with 4.4 percent in younger patients, a significant difference. With nationwide centralization of PD, the in-hospital mortality rate after this procedure decreased. Further centralization of PD is likely to decrease mortality further, especially in the elderly [322].

Evaluation of incidence, treatment, and survival trends after resection of pancreatic cancer at a national level was done using data on patient and tumor characteristics from the nationwide Netherlands Cancer Registry trends were analyzed for the period 1989-2008. A total of 30,025 patients diagnosed with pancreatic cancer were included. The incidence remained stable over the 20-year study period at approximately 9 per 100,000 inhabitants. Resection rates increased from 8 percent in 1989 to 12 percent in 2008, adjuvant chemotherapy rates increased from 7 percent to 29 percent, and palliative chemotherapy rates increased from 5 percent to 19 percent. Relative survival proportions did not change over time; besides a minimal, nonsignificant increase at 3 months from 53 percent to 55 percent, these remained 34 percent at 6 months and 5 percent at 3 years. Among the patients undergoing tumor resection, relative survival increased from 82 percent to 93 percent at 3 months and from 51 percent to 63 percent at 1 year after diagnosis. However, no improvement was seen after 3 years (23 %). The increased short-term survival among patients who underwent resection probably reflects decreased postoperative mortality driven by ongoing centralization efforts. However, longer-term survival remained poor irrespective of the changes in management in the past decades [323].

Health related transitions

Pancreatic cancer is one of the least common tumors, nevertheless it is one of the most lethal. This lethality is mainly due to the fact that the vast majority of patients are diagnosed in an advanced stage. The objective of this work is investigate how different covariates affect the transition to death after a first admission due to pancreatic cancer. It was analyzed the impact of different factors on health related transitions after a first hospital admission related

to pancreatic cancer based on a multi state model. Transitions of interest include the transition to death (i.e. survival time), but also the time between a first admission and discharge or between discharge and readmission. It was considered comorbidities, the type of admission, and especially the performance of pancreas surgery as covariates with a potential effect on the transition intensities. The multi state model allows for a very detailed analysis since all covariate effects may change depending on the current state of the patient [324].

Personalised medicine

Pancreatic cancer has an infaust prognosis and is the fourth commonest cause of cancer related death in men. Design of rational treatment has been hampered by lack of insight into the pathogenesis of the disease. Recently more insight has been gained into a number of crucial aspects of pancreatic carcinogenesis, in particular the cell types that can give rise to oncological transformation in the pancreas, different modes of interaction between transformed pancreatic tumour cells to overcome the pressure of immune surveillance and the various changes in intercellular biochemistry that tumour cells employ to both sustain chemoresistance and metastasis. Although still largely incomplete, this new knowledge opens novel avenues on more successful treatment of the disease through personalised medicine [325].

Cooperation between hospitals

In the face of continuous medical progress on the one hand and the increasing cost pressure through the diagnosis-related groups (DRG) system with concomitant hospital privatization on the other, pioneering and economical models for modern and competent patient care are required. The cooperation model of the surgical department of the Heidelberg University Hospital is based on patient selection according to the grade of disease complexity and has been successfully developed in Heidelberg since 2005. The long-term results on the basis of actual proceeds are presented. Cooperation with the Salem Hospital chaired by the director of the University surgical department has been ongoing for 6 years. General visceral surgery cases with low complexity are treated at the secondary cooperation hospitals whereas complex oncological operations of the esophagus, liver, pancreas, rectum or multivisceral resections and transplantations are performed at the University hospital. Optimal utilization of the operative and infrastructural resources of both cooperation partners lead to an improvement in surgical training and proceeds. Likewise, another cooperation with the secondary hospital in Sinsheim, which started 2 years ago, has shown similar positive results. Clinical rotation for surgical residents and attending surgeons guarantee a complete and competent surgical training in the field of general surgery. It was concluded that the longterm results indicate that the cooperation model functions to achieve an optimized treatment of patients and an economical win-win situation for all cooperation partners by differential utilization of the available resources in the hospital network [326].

Early cancer

Surgery is the cornerstone of potentially curative therapy for upper gastrointestinal cancer. It was analyzed the patterns of treatment regarding the use of surgery for early-stage upper gastrointestinal cancer in the United States. The Surveillance, Epidemiology, and End Research database was used to identify patients with cancer of the esophagus, stomach, pancreas, liver, gallbladder, biliary tract, or duodenum (2004-2007). Only patients with potentially resectable stage I and II disease were selected. The primary outcome measure was the use of curative intent surgery. The secondary outcomes were the predictors of surgery. It was identified 29,249 patients with a median age of 69 years. Only 54 percent of

the patients underwent cancer-directed surgical resection, ranging from 28 percent for liver cancer to 89 percent for gallbladder cancer. The remaining patients underwent either local excision (8 %) or no surgery (38 %). Among the no surgery group, most patients (79 %) were documented as "not being recommended for resection." The independent variables on multivariate analysis predictive of a nonoperative approach included black race, age older than 75 years, tumor size greater than 5 cm, and high poverty level. Patients who did not undergo surgery had worse median and overall survival at 3 years than patients undergoing surgery (11 months versus 36 months and 14 % versus 43 %, respectively). It was concluded that almost one half of patients with early-stage upper gastrointestinal cancer did not receive potentially curative surgery, with an adverse effect on overall survival. A combination of demographic, tumor, and socioeconomic factors were predictive of a lack of surgical resection [327].

Speed of growth

It was investigated pancreatic cancer progression by utilizing a mathematical framework of metastasis formation together with comprehensive data of 228 patients, 101 of whom had autopsies. It was found that pancreatic cancer growth is initially exponential. After estimating the rates of pancreatic cancer growth and dissemination, It was determined that patients likely harbor metastases at diagnosis and predicted the number and size distribution of metastases as well as patient survival. These findings were validated in an independent database. Finally, it was analyzed the effects of different treatment modalities, finding that therapies that efficiently reduce the growth rate of cells earlier in the course of treatment appear to be superior to upfront tumor resection. These predictions can be validated in the clinic. A interdisciplinary approach provides insights into the dynamics of pancreatic cancer metastasis and identifies optimum therapeutic interventions [328].

Perioperative prognosis

Surgical Apgar score

Pancreaticoduodenectomy (PD) remains a procedure that carries considerable morbidity. Numerous studies have evaluated factors to predict patients at risk. The aim of one study was to determine whether the surgical Apgar score (SAS) predicts perioperative morbidity and mortality. It was examined 553 patients undergoing successful PD between 2000 and 2010. Postoperative complications were graded using the Clavien scale, and the SAS (range, 0-10) was determined. The Cochran-Armitage test for trend was used to determine the association between grouped SAS scores (0-2, 3-4, 5-6, 7-8, and 9-10) and each of the outcomes. The average patient age was 64 years, and there was an even distribution of males and females. There were 11 perioperative deaths (2 %), 186 grade 2 or higher complications (34 %), and 86 major complications (grades 3-5, 16 %). Additionally, 61 patients developed pancreatic fistulae (11 %). Statistical analysis determined that SAS was a significant predictor of grade 2 or higher complications, major morbidity, and pancreatic fistula but not mortality. It was demonstrated that the SAS is a significant predictor of perioperative morbidity for patients undergoing PD. This score should be used to identify patients at higher risk in order to prioritize use of postoperative critical care beds and hospital resources [329].

Staging laparoscopy

The role of laparoscopy in staging periampullary malignancies is to detect small-volume metastatic disease not visible on preoperative imaging. Owing to improvements in preoperative imaging, some centers no longer undertake routine laparoscopic staging, whereas others still find it a useful pre-exploration tool. One study investigated the diagnostic yield of staging laparoscopies in 137 consecutive potentially resectable patients with periampullary malignancies. Serology on presentation, tumor size on computed tomography and proinflammatory markers such as C-reactive protein, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and Glasgow Prognostic Score were also examined to see if they were able to identify patients more likely to benefit from staging laparoscopy. Laparoscopy identified occult disease in 16 percent of the patients. Only tumor diameter on cross-sectional imaging was related to an increase in diagnostic yield on staging laparoscopy. Area-undercurve values for tumor size and occult disease at laparoscopy were 0.8. It was concluded that staging laparoscopy is a useful adjunct to computed tomography in staging periampullary cancers. Tumor size (especially >45 mm) is the only preoperative marker predictive of unexpected occult disease and may be used to select high-risk patients for laparoscopic staging [330].

Surgical techniques

Pancreatojejunostomy

There is a high risk of anastomotic leakage following pancreaticojejunostomy after pancreaticoduodenectomy or middle pancreatectomy in patients with a normal soft pancreas because of the abundant exocrine function. Therefore, pancreaticojejunostomy is generally performed using a stent tube (stented method). However, pancreaticojejunostomy with a certain duct-to-mucosa anastomosis does not always require a stent tube even in patients with a normal soft pancreas. It was no presented how to performe pancreaticojejunostomy with duct-to-mucosa anastomosis without a stent tube (nonstented method) and obtaine good results. The objective of this technique is to maintain adequate patency of the anastomosis using a fine atraumatic needle and monofilament suture. The pancreas, including the pancreatic duct, is sharply transected with a scalpel. Any arterial bleeding points on the pancreatic cut end are repaired with fine nonabsorbable sutures. The end-toside anastomosis between the pancreas and jejunum consists of two layers of sutures. The outer layer is composed of the capsular parenchyma of the pancreas and the jejunal seromuscularis, and the inner layer is composed of the pancreatic duct with an adequate pancreatic parenchyma and the whole jejunal wall. Complete pancreaticojejunostomy using duct-to-mucosa anastomosis does not require a stent tube. This non-stented method can be considered one of the basic procedures for pancreaticojejunostomy because of its safety and reliability [331].

Pancreatic anastomotic failure remains the main reason for morbidity and mortality after pancreaticoduodenectomy, and there is no existing flawless pancreaticojejunal reconstruction approach to this date, especially for the normal soft pancreas cases. It was compared a pancreatic stump-closed pancreaticojejunostomy technique (group B; n=33) with conventional duct-to-mucosa fashion (group A; n=30) retrospectively in 63 normal soft pancreatic texture cases. Some operative related data including postoperative complications, anastomosis time, hospital stay days, mortality rate, and relaparotomy rate were analyzed. There was no difference concerning the incidences of postoperative morbidity, including pancreatic fistula, postpancreatectomy hemorrhage, delayed gastric emptying, intra-abdominal abscess, and remnant pancreatitis between two groups. The differences of anastomosis time, hospitalization days, relaparotomy rate, and mortality rate were also not

significant. However, group B patients had a shorter duration for healing of postoperative pancreatic fistula than group A (15 ± 9 versus 33 ± 14 days) For the normal soft pancreas cases, pancreatic stump-closed pancreaticojejunostomy technique is quite safe and convenient according to our experience; ideal clinical results could be achieved with its application in the future [332].

Using a standardized technique for pancreaticojejunostomy that we term "pair-watch suturing technique", we prospectively analyzed the effects of a pancreatic stent tube for preventing pancreatic fistula and furthermore evaluated which perioperative factors had an influence on the development of pancreatic fistula. Before anastomosis, it was imagined the faces of a pair of wristwatches on the jejunal hole and pancreatic duct. The first stitch was put between 9 o'clock on the pancreatic side and 3 o'clock on the jejunal side, and a total of 7 stitches were put in the posterior wall, followed by 5 stitches in the anterior wall. Using this technique, twelve stitches can be sutured in the first layer anastomosis regardless of the caliber of the pancreatic duct. From 2007 to 2009, 55 consecutive patients who underwent the pair-watch suturing technique were divided into two groups: stent (n=28) and no-stent (n=27). The incidence rate of pancreatic fistula was statistically analyzed. From 2007 to 2011, 102 consecutive patients were retrospectively divided into two groups according to the International Study Group on Pancreatic Fistula criteria: postoperative pancreatic fistula (POPF) and non-POPF. Perioperative factors were almost the same between the stent and no-stent groups, and the incidence of pancreatic fistula was very similar: 10 percent in the stent group and 15 percent in the no-stent group. Additionally, all patients who developed pancreatic fistula belonged to grade A. Among 102 patients, 15 (15 %) were identified as having pancreatic fistula: 9 (9 %) in grade A, 5 (5 %) in grade B, and 1 (1 %) in grade C. Comparing the POPF and non-POPF groups, it could not br detected any significant risk factors for the development of pancreatic fistula. It was considered that the pair-watch suturing technique is less susceptible to any factors, providing reliable anastomosis for any size of pancreatic duct and any texture of remnant pancreas [333].

Pancreatogastrostomy

Pancreatic anastomotic leakage remains a persistent problem after pancreaticoduodenectomy (PD), especially in the presence of a soft, nonfibrotic pancreas. Pancreatic leakage remains a common and serious complication after standard pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD). Pancreatic fistula is occasionally followed by several other potentially life-threatening complications, such as massive hemorrhage of eroded vessels and peritonitis. To prevent these complications, two main anastomotic techniques for reconstruction after PD, pancreaticojejunostomy (PJ), and pancreaticogastrostomy (PG), exist. According to four randomized trials comparing PJ and PG, there is no difference regarding the prevalence of pancreatic fistula between these reconstruction techniques. However, since the first clinical application of PG performed by Waugh and Clagett in 1946 pancreaticogastrostomy (PG) is a favoured reconstruction procedure of several surgeons after pancreaticoduodenectomy as PG has some theoretical and technical advantages over PJ. First, the anastomosis can be created easily because of the proximity of the stomach and the pancreas remnant. Second, the thick posterior gastric wall is an excellent suture bed with an excellent blood supply. Third, the pancreatic juice is not activated because of the acid milieu and lack of enterokinases in the stomach. Fourth, if a minor dehiscence of the PG occurs, it can be managed in many cases via endoscopic interventions, for instance, fibrin sealing. Recently published studies on PG had shown that the prevalence of pancreatic fistula ranged from 0 to 16%, and the mortality rate varied from 0 to 12 percent in studies with 41 up to 250 patients. However, in these studies, the definition of pancreatic fistula was very heterogeneous and mostly not well defined. Several different methods of anastomosing the pancreas to the stomach have been employed, including PG using several mattress sutures and the so-called binding PG using two purse-string sutures at the posterior gastric wall. It was now reported the early results of a new technique for PG,

which combines one binding purse-string and two transfixing mattress sutures between the pancreatic stump and the posterior gastric wall. After the pancreaticoduodenectomy, any bleedings from the cut surface of the pancreatic stump were stopped by bipolar electrical coagulation or absorbable sutures. Then the pancreatic remnant was mobilized 2 to 3 cm from the splenic vein and the surrounding tissues. A polyethylene 5 cm pancreatic tube, 5.0 or 7.5 French was introduced into the main pancreatic duct to insure its patency. This lost drain was fixed to the main pancreatic duct by a 5.0 absorbable suture. Two transient vicryl holding sutures were positioned at the cranial and caudal proximal end of the pancreatic remnant. Then a transverse full-thickness incision was made on the posterior wall of the stomach with a length of at most 2 cm, to ensure tight adherence of the gastric wall to the pancreatic remnant after completion of anastomosis. The appropriate position of the incision was selected, so that the pancreatic stump could enter this hole without tension. Then a 5cm longitudinal incision was created in the anterior gastric wall opposite to the dorsal wall incision. Through the incision of the anterior gastric wall, a full-thickness purse-string suture PDS II 2.0, taking about 1 cm of the whole posterior gastric wall, was preplaced. The pancreatic remnant was then pulled with slide tension on the holding sutures through the whole in the posterior gastric wall into the stomach. This manoeuvre was performed very gently to ensure tight wrapping of the posterior gastric wall around the pancreatic remnant and to avoid laceration of the pancreas. Ideally, the pancreatic remnant should protrude above the posterior gastric wall by 2 cm. Afterwards mattress sutures were preplaced through the posterior gastric wall and the pancreas, one cranial and one caudal of the main pancreatic duct. These sutures were carried out with double-armed straight needles passing in an U-like fashion. Each U-like suture runs from the mucosal surface to the serosal surface of the caudal posterior gastric wall, just above the preplaced purse-string suture, then straight through the ventral to the dorsal surface of the pancreas, and finally from the serosal surface to the mucosal surface of the cranial posterior gastric wall. The threads near the centre of the pancreatic stump were placed carefully to avoid passing through the main pancreatic duct containing the catheter. First the U-like mattress sutures and then the pursestring suture were ligated. The gastrostomy on the anterior gastric wall was closed with all layer single sutures PDS II 2-0. An end-to-side hepaticojejunostomy and antecolic end-toside gastrojejunostomy in case of standard PD or antecolic duodenojejunostomy in case of PPPD were performed to complete the reconstruction. This technique was applied in 35 patients after PD for malignant and benign diseases of whom 10 (29 %) had a soft pancreas. Median time for the anastomosis was 18 minutes. Operative mortality was zero, and morbidity was 34 percent. Three (9 %) patients developed a pancreatic fistula (2 type A, 1 type B) as classified according to the International Study Group on pancreatic fistula. All fistulas resolved without further intervention. The described technique is a simple and safe reconstruction procedure after PD that warrants further evaluation [334].

Pancreatic fistula still remains a persistent problem after pancreaticoduodenectomy. We have devised a pancreas-transfixing suture method of pancreaticogastrostomy with duct-to-mucosa anastomosis. This technique is simple and reduces the risk of pancreatic leakage by decreasing the risk of suture injury of the pancreas and by embedding the transected stump into the wall of the stomach. This novel technique of pancreaticogastrostomy is an effective reconstructive procedure following pancreaticoduodenectomy, especially for patients with a soft and fragile pancreas [335].

Experimental pancreaticojejunostomy

Various anastomosis techniques have been introduced for the safe pancreaticoenterostomy. In the present study, it was developed an experimental animal model for simple pancreaticojejunostomy and evaluated the feasibility, safety, and efficacy of this technique. Ten dogs underwent the simple approximation ("docking") method for pancreaticojejunostomy and were re-explored on the 30th post-operative day. After excision of the remnant pancreas with the jejunal segment of the pancreaticojejunostomy, the degrees of fibrosis in the remnant pancreas were analyzed according to the patency of the pancreaticojejunostomy. There were no mortalities and clinically significant complications. The patency of pancreaticojejunostomy remained in six cases and was obliterated in four cases. It was noted that obliterated pancreaticojejunostomy accompanied cases with more dilated pancreatic ducts. The grade of pancreatic fibrosis was significantly correlated with the obliterated pancreaticojejunostomy and the size change of the remnant pancreatic duct. The suggested simple pancreaticojejunostomy method is easy and shows no evidence of significant pancreatic fistula. However, the potential risk of dysfunction in the remnant pancreas limits its possible clinical applications. The meticulous duct-to-mucosa pancreaticojejunostomy is highly preferred to manage the remnant pancreas following pancreaticoduodenectomy [336].

Proximal gastrojejunal reconstruction

Endoscopic access of the bile duct and pancreatic duct is difficult and unsuccessful in up to 50-70 percent of cases after Billroth II or Roux-en-Y reconstruction. Reconstruction after resection is invariably done by proximal biliary and pancreatic enteric anastomoses and distal gastric or duodenal enteric anastomoses. Proximal placement of the gastro or duodenal jejunal anastomosis is neither advocated nor reported because of unsubstantiated concern that a pancreatic or bile leak distal to the stomach or duodenum would cause sepsis or cholangitis, delay oral feeding, and prolong hospitalization. This has been a long-standing, oral, preceptor-based surgical tradition. An extensive literature search of published case reports and case series as well as retrospective and prospective studies over the past 10 years did not result in any citations referencing proximal placement of the gastroenteric anastomosis during pancreaticoduodenal resection. There has been little reason or need to question this since ERCP after pancreaticoduodenal resection for pancreatic cancer is infrequently needed. Despite absence of supporting literature this is done for alleged fears of pancreatic and biliary fistulas that will delay oral feedings and prolong hospitalization. With more pancreaticoduodenal resection being done for premalignant and malignant pancreatic cystic and ductal lesions, surveillance of the remnant pancreatic duct mucosa for multicentricity may be necessary. Reconstruction by proximal gastrojejunostomy, and distal biliary and pancreatic anastomoses is infrequently used after resection of the head of the pancreas because of fear of fistulas and cholangitis. Because of this there is a need for endoscopic visualization and biopsy of the residual pancreatic duct, since multi-centricity is characteristic of some of these malignancies. Since endoscopic access of the bile duct and pancreatic duct is difficult and unsuccessful in 50-70 percent after B II or Roux Y reconstruction, it was prospectively studied the merit and complications (early and late) of proximal gastrojejunal (PGJ) reconstruction after pancreaticoduodenal resection. Thirty-nine consecutive, non-randomized patients underwent pancreaticoduodenectomy and PGJ reconstruction over 14 months. There were 21 males and 18 females. Seven patients with IPMN underwent repeat CT scanning for surveillance, with 3 requiring repeat EUS and ERCP. There were no technical difficulties accessing the pancreas or the pancreatic duct, supporting the PGJ reconstruction. It was concluded that proximal gastrojejunal reconstruction following pancreaticoduodenal resection may be safely done with similar morbidity to traditional pancreaticojejunal reconstructions. PGJ reconstruction may be of greater value when direct visual access to the bile duct or pancreatic duct is necessary, and should be considered when doing resection for mucinous cysts or IPMN of the head of the pancreas [337].

Pancreatoduodenectomy in patients with liver cirrhosis

Liver cirrhosis is considered to be a contraindication for pancreaticoduodenectomy (PD). The aim of one study was to present 4 cases of successful PD in cirrhotic patients. Among the charts of 90 patients who underwent PD between 2004 and 2008, 4 patients with liver cirrhosis were retrospectively reviewed. There were 3 males and 1 female, aged from 53 to
66 years, who underwent PD for pancreatic head adenocarcinoma (n=3) or ampullary carcinoma (n=1). The median tumor size was 21 mm (18-26) and 2 patients had preoperative biliary drainage. All patients had biopsy showing cancer prior to the operation. Cirrhosis was preoperatively suspected due to chronic alcoholism or liver dismorphy on CTscan and confirmed histologically in all patients. All patients were Child Pugh A without portal hypertension. The median operating time was 575 minutes (480-600) and 2 patients received an intraoperative blood transfusion. No patient died postoperatively. All patients had postoperative complications: ascites (n=2), pancreatic fistula (soft pancreas) (n=2) and pulmonary infection (n=1). There was neither liver failure nor postoperative bleeding. Two patients required re-operation for suspected mesenteric ischemia (n=1) and pancreatic fistula (n=1). The median length of hospitalization was 50 days (41-74). The median survival was 13 months (3 patients are alive and disease free). The data shows that PD in patients with Child A liver cirrhosis should not be systematically considered as a contraindication [338].

Total pancreatectomy

It was described a patient presenting with a resectable carcinoma of the remnant pancreas at 3 years after undergoing a pylorus-preserving pancreaticoduodenectomy for invasive ductal carcinoma of the pancreatic head. It was also performed a distal pancreas autotransplantation using a part of the resected pancreas to preserve endocrine function. Final histologic findings showed the second tumor to be an invasive ductal carcinoma consisting of a well-differentiated tubular adenocarcinoma with similar histopathologic findings as the first tumor. There were no microscopic lymph node metastases and no evidence of microvascular invasion (pStage IA [pT1, pN0, M0] and R0 according to the International Union Against Cancer TNM classification). The patient was discharged at 20 days after surgery without any trouble and followed by adjuvant chemotherapy with S-1. The carbohydrate antigen 19-9 value was again normalized after the second surgery. Twenty months after the second operation, the patient is alive without cancer recurrence. The pancreas graft is functioning with a blood glucose of 108 mg/dL, HbA1C of 6.2 percent, and serum C-peptide of 1.4 ng/mL [339].

Total mesopancreas excision (TMpE)

Retro pancreatic invasion is a major concern in pancreatic head carcinoma. Posterior clearance has been recognized as an independent risk factor for disease recurrence and hence patient survival. The aim of this study was to report a standardized method that ensures posterior clearance with Total Mesopancreas Excision (TMpE). The procedure consisted in a posterior approach with cranio-caudal dissection at the origin of the superior mesenteric artery and the celiac trunk all along their right semi-circumference. This allowed a complete clearance of retro pancreatic tissues with safe control of pancreaticoduodenal arteries at their origin. Fifty-two consecutive pancreatic resections with TMpE were performed. Sixteen cases were associated to vascular resection. Pathology revealed an adenocarcinoma of the pancreatic duct, distal bile duct, periampullary and neuroendocrine carcinoma. Mesopancreas was invaded by cancer in 12 cases, of these, 3 had invaded margins and 7 had a margin less than 1 mm. Mesopancreas was the only site of tumour infiltration. Applying the International Union Against Cancer criteria, an R0 resection was thus achieved in 42 patients. The procedure is feasible and safe in experienced hand. It is a description of a standardized method for TMpE that clearly shows an advantage in improving posterior clearance and R0 resection [340].

Central pancreatectomy

Middle pancreatectomy is parenchyma- and adjacent organ-sparing pancreatectomy indicated for small tumors located in the body, but deeply located in the gland, and therefore

hard to enucleate. Others lesions including pancreatic trauma or arteriovenous malformation are also candidate targets. Invasive ductal carcinoma, even when the tumor is small enough, is not eligible because the most of these tumors show extrapancreatic invasion. After exposure of neck to body of the pancreas, middle pancreatectomy was performed by proximal and distal transection, reconstruction after Roux-Y pancreaticojejunostomy, which is the most common. This procedure is low-invasive and allow the preservation of exocrine and endocrine pancreatic function without loss of duodenal passage, however, it also has a high morbidity associated with pancreatic fistula. One article provided indications and surgical techniques with special focus on the procedure of middle pancreatectomy [341].

Central pancreatectomy is a pancreas-sparing alternative to standard pancreatic resections in selected cases. Although associated with high morbidity, the risk factors for surgical complications of this procedure are not yet defined. The clinicopathological and perioperative data of 24 patients who underwent central pancreatectomies (2002-2010) were correlated with surgical complications. The overall morbidity rate was 54 percent (pancreatic fistula, 40 %). In a univariate analysis, age over 40 years, body mass index \geq 30 kg/m², smoking and American Society of Anesthesiologists III scores were significantly correlated with increased morbidity. In a multivariate analysis, a significant correlation with the development of complications was found for body mass index \geq 30 kg/m² and age over 40 years. It was concluded that certain patient-related factors (older age, obesity and smoking) appear to have a negative impact on early postoperative outcome after central pancreatectomy. For patients with these factors, an alternative distal pancreatectomy should be considered. Central pancreatectomy should be tailored not only to the pathology but also to the patient profile [342].

Meso-pancreatectomy

In 1957, Guillemin and Bessot first performed a central segmental pancreatic resection with an anastomosis to both pancreatic stumps with an omega-shaped jejunal loop in a patient with chronic pancreatitis. Two years later, Letton and Wilson performed, in 2 cases of severe traumatic injury of the pancreatic body, a Roux-en-Y jejunal loop anastomosis to the tail of the pancreas and a blind closure of the pancreatic head remnant instead of a distal pancreatectomy with splenectomy. It was now reported, for the first time, a new reconstructive procedure using a pancreatic stent tube after median segmental pancreatectomy for pancreatic endocrine tumor. This technique allows a clean operation, can avert the complications related to a hypothetical stenosis or leak of the proximal pancreatic duct, and can make it easier to treat complications such as pancreatic fistula. The lesser sac was entered and the anterior aspect of the pancreas was widely exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Intraoperative pancreatic ultrasound was performed to delineate the lesion better and to exclude concomitant lesions that might have necessitated a change in plan. Intraoperative pancreatic ultrasound confirmed a 1.2-cm nodular hypoechoic lesion with irregular borders in the pancreatic body. The pancreas was elevated off the superior mesenteric vein-portal vein venous trunk. Stay sutures were placed in the superior and inferior pancreatic margin to indicate the proximal and distal limits of the division and to aid in the subsequent dissection of the pancreas from the splenic vein. The pancreas was divided proximally with a scalpel blade at least 1 cm from the lesion. The distal stump was gently retracted toward the left to allow the cautious and tedious process of freeing the splenic vein from the posterior surface, as well as clipping and cutting all of the fine venous tributaries lying between the splenic vein and the pancreas. This maneuver allowed to slide the distal stump toward the proximal stump and make the anastomosis easier. The pancreas was divided with a scalpel blade distally to the lesion. The specimen was then sent to the pathologist for frozen section examination to confirm the diagnosis and that the margins of the resections were cleared. Reconstruction was accomplished with a pancreatic end-to-end anastomosis with duct-toduct anastomosis. Pancreatic ductal anastomosis was constructed using interrupted absorbable monofilament sutures (PDS 6-0), and pancreatic parenchymal anastomosis was performed with absorbable interrupted monofilament sutures (PDS 3-0). After having performed the anastomosis of the posterior wall of the parenchyma and the pancreatic ductal anastomosis, it was inserted a pancreatic stent tube into the pancreatic duct (5F diameter) with multiple perforations. The tube was without perforations within 1 cm from the proximal and distal end of the anastomosis to keep the suture dry. This pancreatic duct tube was then dragged into the duodenum and a stitch (PDS 6-0) was inserted between the anterior wall of the external part of the tube and the anterior wall of the distal pancreatic duct (cut face) to keep it in place. The reconstruction was than completed and a fibrinogen/thrombin-coated [collagen patch was sprayed onto the anastomosis site [343].

Tumors of the neck of the pancreas with venous invasion

Tumors of the neck of the pancreas may involve the superior mesenteric and portal veins as well as the termination of the splenic vein. This presents a difficult problem since the pancreas cannot be transected through the neck as is standard in a Whipple procedure. Here, it was presented a method of resecting such tumors, which was termed "Whipple at the Splenic Artery (WATSA)". The pancreas and splenic vein are divided just to the right of the point that the splenic artery contacts the superior border of the pancreas. This plane of transection is approximately 2 cm to the left of the pancreatic neck and away from the tumor. The superior mesenteric artery is cleared from the left side of the patient. With the specimen remaining attached only by the superior mesenteric and portal veins, these structures are clamped and divided. Reconstruction is performed with or without a superficial femoral vein graft. The splenic vein is not reconstructed. Ten cases were performed without mortality. It was previously shown that the pattern of venous collateral development following occlusion of the termination of the splenic vein in the manner described is not similar to that of cases of sinistral (left sided) portal hypertension. Whipple at the splenic artery (WATSA) is thus a safe method for resection of tumors of the neck of the pancreas with vein involvement. It should be performed in high-volume pancreatic surgery centers [344].

Extended lymph node resection

The value of pancreatoduodenectomy (PD) with extended lymphadenectomy for pancreatic cancer has been evaluated by many retrospective studies and 3 randomized controlled trials (RCT). However, the protocols used and the results found in the 3 RCTs were diverse. Therefore, a multicenter RCT was proposed in 1998 to evaluate the primary end point of long-term survival and the secondary end points of morbidity, mortality and quality of life of patients undergoing standard versus extended lymphadenectomy in radical PD for pancreatic cancer. From 2000 to 2003, 112 patients with potentially curable pancreatic head cancer were enrolled and intraoperatively randomized to a standard or extended lymphadenectomy group. No resected patients received any adjuvant treatments. A hundred and one eligible patients were analyzed. Demographic and histopathological characteristics of the two groups were similar. The mean operating time, intraoperative blood loss and number of retrieved lymph nodes were greater in the extended group, but the other operative results were comparable. Although this multicenter RCT was conducted in a strict setting, extended lymphadenectomy in radical PD did not benefit long-term survival in patients with resectable pancreatic head cancer and led to levels of morbidity, mortality and quality of life comparable to those found after standard lymphadenectomy [345].

Hepatic artery reconstruction

Hepatic artery (HA) reconstruction is an important part of resective surgery for advanced hepatobiliary and pancreatic malignancies, but few reports have been published. To identify indications for HA reconstruction, it was retrospectively analyzed the surgical procedures and outcomes. En-bloc resection of advanced hepatobiliary and pancreatic malignancies followed

by HA reconstruction was performed in 35 patients. Patients ranged in age from 27 to 81 years and included 18 men and 17 women. The primary site of cancer included the bile duct in 22 patients, the pancreas in 7, and others in 6. Reconstruction of the HA was necessitated by HA resection due to direct cancer invasion in 29 patients and by accidental arterial injury during surgical procedure in 6 patients. The HA was reconstructed with end-to-end anastomosis between hepatic arteries in 17 patients. Transposition of an intra-abdominal artery, such as the gastroepiploic artery, was required in 14 patients, and arterial grafting was required in 4 patients. Although the HA patency was achieved in 30 patients, 4 cases of arterial thrombosis and 1 case of arterial rupture developed postoperatively. The overall RFS time was analyzed in all patients, and mean and median RFS times were 18 and 9 months, respectively. Although oncologic outcomes remain poor, HA resection and reconstruction can be performed in selected patients. We believe that the method of first choice for HA reconstruction is end-to-end anastomosis between HAs. A vascular autograft should be used only in selected cases [346].

Preservation of the posterior epiploic artery

The patient was a 56-year-old man who had previously undergone a total gastrectomy without splenectomy, and was diagnosed with pancreatic head and body cancers and primary solitary lung cancer. The pancreas body tumor invaded the origin of the splenic artery, and if the origin of the splenic artery were resected there would be no blood flow to the pancreas tail, resulting in a need for total pancreatectomy. However, it was focused on the posterior epiploic artery (PEA), which is a less well known blood supply from the mesocolon to pancreatic body and tail, and planned to preserve the pancreatic tail as long as the resected margin of the pancreas was not malignant, considering his limited life expectancy. It was performed a pancreaticoduodenectomy with resection of the origin of the splenic artery preserving the pancreatic tail and PEA. The patient has been free from insulin therapy for blood sugar control, and has been well for 10 months after the surgery [347].

Preoperative embolization of replaced right hepatic artery

Aberrancy of the hepatic arterial anatomy is common. Because of its course directly adjacent to the head of the pancreas, a replaced right hepatic artery (RHA) is vulnerable to invasion by peri-pancreatic malignancies. Division of the RHA at the time of pancreaticoduodenectomy, however, may result in hepatic infarction and/or bilioenteric anastomotic complications. It was reported two cases of patients undergoing preoperative embolization of tumor encased replaced RHAs to allow for sufficient collateralization prior to pancreaticoduodenectomy [348].

Portal vein resection

In many patients with pancreatic cancer, PV resection is necessary to increase resectability and obtain cancer-free margins. A retrospective study was performed to clarify the correlation between radiographic type of portal vein (PV) invasion and pathological grade of PV wall invasion, and their correlation with postoperative prognosis. It was analyzed 671 patients who had undergone surgery for invasive adenocarcinoma of the pancreas between 1981 and 2010. Radiographic types of PV invasion of pancreatic head cancer were classified into A (normal), B (unilateral narrowing), C (bilateral narrowing), or D (complete obstruction with collateral veins), by portography or computed tomography. Pathological grades of PV wall invasion were classified as 0 (no invasion), 1 (tunica adventitia), 2 (tunica media), or 3 (tunica intima). Four hundred and sixty-three patients underwent resection, and PV resection was performed in 297. Combined arterial vessel resection was performed in 16 cases. No significant difference in operative mortality was observed between PV preservation (0.6 %) and PV-only resection (2.1 %), and no operative deaths occurred after 1999. Radiographic classification of PV invasion correlated with incidence of pathological PV wall invasion. In pancreatic head carcinoma, no pathological PV wall invasion was observed in type A (n=111). Pathological PV invasion was observed in 51 percent of type B (42/82), 74 percent of type C (72/97), and 93 percent of type D (63/68). Long-term survival (>5 years) was observed in types A and B, and grades 0 and 1 subgroups. It was concluded that even in radiographic classification type B, pathological PV wall invasion was observed in 51 percent of patients. Long-term survival was observed in types A and B, and grades 0 and 1 [349].

The purpose of one study was to determine the significance of portal vein-superior mesenteric vein (PV-SMV) invasion on survival in patients who underwent margin-negative pancreatoduodenectomy (PD) with PV-SMV resection for pancreatic adenocarcinoma. It was retrospectively reviewed the records of 60 patients who underwent margin-negative PD with or without PV-SMV resection for pancreatic adenocarcinoma between 2001 and 2007. The depth of vessel invasion was investigated and was categorized into 3 groups: tunica adventitia, media, and intima. Clinicopathologic factors and survival were analyzed. Portal vein-superior mesenteric vein resection was performed on 19 patients, but only 15 patients (79 %) had histologically true invasion and showed poorer survival (median survival, 14 vs 9 months). Univariate analysis revealed that poorly differentiated tumor, lymphatic invasion, endovascular invasion, PV-SMV invasion, and invasion into the intima of PV-SMV were statistically significant. Poorly differentiated tumor and invasion into the intima of PV-SMV were significant in multivariate analysis. It was concluded that aggressive surgical resection should be attempted in cases with suspected PV-SMV invasion because 21 percent of patients had no true invasion and showed better survival than those with true invasion. However, invasion into the tunica intima may be a poor prognostic factor for survival even after margin-negative PD for pancreatic adenocarcinoma [350].

Survival rates after surgery and adjuvant chemotherapy for pancreatic ductal adenocarcinoma (PDA) remain low. Selected patients with portal/superior mesenteric vein (PV) involvement undergo PV resection at pancreaticoduodenectomy (PD). One study analyseed outcomes for PD with/without PV resection in patients with PDA. A retrospective analysis of prospectively collected data on patients requiring PD for histologically proven adenocarcinoma between 1/1997 and 9/2009 identified 326 patients with PDA, with 51 requiring PD with PV resection. Patients were analyzed in two groups: PD + PV resection vs. PD alone. Multivariate analysis was used to identify predictive variables influencing survival and the Kaplan-Meier method to estimate patient survival. Mean age for patients with PV resection was 66 (range 46-80) years, 47 percent were male. Both groups had similar patient demographics, perioperative and tumor characteristics. Postoperative morbidity was similar for patients with and without PV resection (28 vs 28 %). Thirty-day mortality was significantly higher in patients with PV resection (14 %) vs. PD alone (5 %). Overall survival however was similar in both groups (median PD alone 15 months vs 15 months PD + PV). Multivariate analysis identified age, tumor grading, stay on the ICU and lack of chemotherapy as independent risk factors for reduced long-term survival. It was concluded that in carefully selected patients, PV resection results in similar long-term survival compared to PD alone. In selected patients, PV infiltration may be considered a sign of anatomical proximity of the tumor, rather than only a sign of increased tumor aggressiveness [351].

External stent drainage of the pancreatic duct

Postoperative pancreatic fistula (POPF) remains one of the most common causes of morbidity following pancreaticoduodenectomy (PD). One randomized trial examined whether external stent drainage of the pancreatic duct decreases the rate of POPF after PD and subsequent pancreaticojejunostomy (PJ). Consecutive patients who underwent PD with subsequent construction of a duct-to-mucosa PJ were randomized into a stented and a non-stented group. The primary outcome was the incidence of clinically relevant POPF.

Secondary outcomes were morbidity and mortality rates, and hospital stay. Of 114 PD procedures, 93 were suitable for inclusion in the study after informed consent. The rate of clinically relevant POPF was significantly lower in the stented group than in the non-stented group: three of 47 (6 %) versus ten of 46 (22 %). Among patients with a dilated duct, rates of POPF were similar in both groups. Among patients with a non-dilated duct, clinically relevant POPF was significantly less common in the stented group than in the non-stented group: two of 21 (10 %) versus eight of 20 (40 %). No significant differences in morbidity or mortality were observed. Univariable analysis identified body mass index (BMI), pancreatic cancer, pancreatic texture, pancreatic duct size and duct stenting as risk factors related to clinically relevant POPF. Multivariable analysis taking these five factors into account identified high BMI (risk ratio (RR) 11.45), non-dilated duct (RR 5.33) and no stent (RR 10.38) as significant risk factors. It was concluded that external duct stenting reduced the risk of clinically relevant POPF after PD and subsequent duct-to-mucosa PJ [352].

Laparoscopy

Laparoscopic pancreatic surgery is not common practice in Germany and is only carried out in approximately 20 clinics but with an increasing trend. The reasons for this are manifold, such as the current selection of patients and both skills in laparoscopic and pancreatic surgery are necessary to perform this operation safely. In 2008 a registry called "Laparoscopic pancreatic surgery" was implemented to collect enough data in Germany to find out whether the resection is safe, feasible and beneficial for the patient.For further development of new laparoscopic techniques new data is needed. A group of experts performing laparoscopic pancreatic surgery in Germany supplied their data for the German registry for laparoscopic pancreatic resection and a consensus conference about the indications became necessary. This consensus conference discussed in particular the indications for laparoscopic pancreatic resection. A consensus was found by all members of the conference utilizing currently available evidence-based data.It was suggested that all data of laparoscopic pancreatic surgery should be evaluated in the German Registry. A consensus was made which diseases were either suitable for laparoscopic resection or not suitable or suitable in selected cases [353].

The role of laparoscopic resection in patients with pancreatic cancer remains to be clarified, because previous reports have not clearly defined oncologic outcomes. The objective of the present study was to investigate this guestion with the rate of R0 resection and long-term survival as endpoints. The retrospective observational study included prospectively collected data from 40 patients operated laparoscopically with curative intent for exocrine pancreatic malignancies identified among 250 consecutive patients undergoing laparoscopic pancreatic operations since 1997. All 40 patients had histologically verified exocrine pancreatic carcinoma. Ten patients (25 %) with typical ductal adenocarcinoma of the pancreas were deemed nonresectable by laparoscopic staging. Laparoscopic distal pancreatectomy was performed in 29 patients; 8 resections were combined with resections of adjacent organs and 1 removal of a malignant intraductal papillary mucinous neoplasm what appeared to be ectopic pancreatic tissue. In 1 patient, the resection was completed by hand-assisted technique, and 1 procedure was converted to open resection. Postoperative morbidity was 23 percent (n=7). The median hospital stay was 5 days (range, 1-30). The rate of R0 resections was 93 percent. Postoperative 3-year survivals rates were 36 percent for the entire cohort (n=30) and 30 percent in typical ductal adenocarcinoma (n=21). It was concluded that laparoscopic distal pancreatectomy for exocrine pancreatic carcinoma is comparable with outcomes after open surgery and supports the concept that laparoscopic distal pancreatectomy is a safe, oncologic procedure [354].

Laparoscopic distal pancreatectomy RF-assisted

Despite technological improvements in pancreatic surgery, the incidence and morbidity of pancreatic leak after resection of distal pancreas are persistently high in most series.

Laparoscopic distal pancreatectomy (LDP) is today the gold standard procedure for benign and certain malignant neoplasms of the pancreatic body and tail in specialized centers. This study evaluated safety and feasibility of a radiofrequency (RF)-assisted transection device in a porcine model of LDP. LDP was performed on 10 pigs (median weight, 39.6 kg) using a new device based on an internally cooled RF-assisted electrode (Coolinside(®), Apeiron Medical, Valencia, Spain). The animals were subjected to daily observation and then sacrificed and necropsied at 4 weeks postoperatively. Primary end points were the development of postoperative pancreatic fistula using the Pancreatic Anastomotic Leak Study Group definition and/or the presence of abdominal amylase-rich fluid collections or abscesses during necropsy and pathological study and/or dye extravasation from the pancreatic remnant duct. Secondary end points were intra- or postoperative complications, surgery, and transection duration. No clinically relevant postoperative pancreatic fistulas were observed. In one case a grade A postoperative fistula was diagnosed due to amylase drain concentration of more than 6200 IU/mL on postoperative day 4. Median peritoneal liquid amylase concentration on postoperative day 4 was 2399.0 IU/L (range, 819-7122 IU/L), similar to the median plasma amylase level of 1521 IU/L (range, 1015-4057 IU/L). Median surgery time was 93.5 minutes (range, 46-140 minutes), and median transection time was 5 minutes (range, 2-26 minutes). There was one postoperative wound infection. There were no postoperative deaths or major complications. During the histopathological study, the surgical margin of the remaining pancreas showed a common pattern with a central area of necrosis surrounded by granulomatous infiltrate and fibrosis. Ductal obliteration was observed. No purulent inflammatory infiltrate or abscesses were present. Thus, experimental findings suggest that performing pancreatic transection with Coolinside in a animal model of LDP is feasible and safe [355].

Laparoscopic partial pancreatoduodenectomy

Minimally invasive surgery has conquered almost all niches of abdominal surgery. Even though some surgeons have shown equal lymph node ratio and oncologic radicality for laparoscopic surgery of pancreatic cancer, oncologic surgeons still take reasonably conservative views of the use of minimally invasive techniques for the treatment of pancreatic cancer, especially if located in the head of the pancreas. Laparoscopic abdominal approaches on the other hand have a potential advantage of better visualization, decreased postoperative pain, decreased use of analgetics, and shorter hospital stay. It was demonstrated in this technical surgical report the first description of a total laparoscopic pancreatoduodenectomy and reconstruction via laparoscopic pancreatogastrostomy in a 74-year-old female patient with a periampullary tumor. After pylorus-preserving pancreato-duodenectomy by superior mesenteric artery, first approach including standard lymphadenectomy, the reconstruction involved total laparoscopic end-to-side running-suture hepaticojejunostomy, double-layer running-suture antecolic pylorojejunostomy to the first jejunal loop, and pancreatogastrostomy via posterior gastrotomy secured by two anchoring and purse-string sutures [356].

Pylorus-preserving pancreatoduodenectomy

Few reports describe the use of laparoscopic pylorus-preserving pancreaticoduodenectomy (LPPPD) in centers with experience using this technique. In addition, the clinical outcomes of this procedure remain undetermined. In one study, 100 patients with benign or malignant lesions in the pancreatic head underwent LPPPD between 2007 and 2011. The overall clinical outcomes and changes in these outcomes during the surgeon learning period were analyzed to assess the feasibility and safety of this procedure. Pathologic examination of the pancreas confirmed intraductal papillary mucinous neoplasms in 37 patients, solid pseudopapillary tumors in 17 patients, neuroendocrine tumors in 15 patients, serous cystic neoplasms in seven patients, pancreatic ductal adenocarcinomas in seven patients, ampulla of Vater tumors and duodenal gastrointestinal stromal tumors in five patients, and other disease in seven patients. The median operative time was 7.9 h, which decreased with accumulating experience of the surgeon using this procedure, from 9.8 h for the first 33

cases to 6.6 h for the last 34 cases. Complications developed in 25 percent of the patients, including six cases (6 %) with significant pancreatic fistula (International Study Group on Pancreatic Fistula, ISGPF, grade B). The complication rate decreased from 33 percent for the first 33 cases to 18 percent for the last 34 cases. The mean hospital stay was 14 days, which also decreased from 20 days for the first 33 cases to 12 days for the last 34 cases. For the 12 patients in the study cohort with invasive malignant disease, the median tumor size was 2.8 cm, and the median number of lymph nodes harvested was 13. All the patients had margin-negative R0 resections. The LPPPD procedure is technically safe and feasible, with an acceptable rate of morbidity and other clinical outcomes for benign and malignant diseases. Clinical outcomes can be improved once a learning curve has been overcome [357].

Robot-assisted pancreaticoduodenectomy

There are many theoretical advantages that a minimally invasive approach to the pancreaticoduodenectomy might offer patients with benign and malignant disease of the head of the pancreas over traditional open techniques, including improved recovery time. decreased hospital stay, and earlier initiation of and higher rate of completion of adjuvant therapy. The goal of one study was to assess the oncologic and safety outcomes after a robot-assisted approach to pancreaticoduodenectomy. A retrospective review of a prospectively acquired database of robot-assisted pancreaticoduodenectomy (RAPD) for periampullary lesions between 2008 and 2010 was done. Fifty patients underwent attempted RAPD. Conversion to open procedure was required in eight patients (16%). At intention-totreat analysis, pancreatic fistula as defined by the International Study Group of Pancreatic Surgery occurred in 10 patients (20 %). Most patients experienced either no (21, 42 %) postoperative complications or minor Clavien I/II events (13, 26 %). Major morbidity (Clavien III/IV) occurred in 15 patients (30 %). The margin-negative resection rate was 89 percent, and the median number of lymph nodes collected was 18. Fifteen patients met the eligibility criteria for adjuvant chemotherapy after surgery. Eleven (73 %) of 15 eligible patients were treated with adjuvant therapy at a mean of 12 weeks after surgery. It was concluded that RAPD can be performed with safety and oncologic outcomes comparable to open or laparoscopic approaches. Results of this early series suggest that the robot-assisted approach holds promise. Larger, more mature multi-institutional cohorts will be needed to explore potential benefits over open and laparoscopic techniques [358].

Bipolar radiofrequency in parenchymal transection

Intraoperative blood loss has been shown to be an important factor correlating with increased morbidity and mortality in oncological surgery. Despite technological advances in parenchymal transection devices, bleeding remains the single most important complication. To address this, we designed and developed a bipolar radiofrequency (RF) device, the Habib 4X (Angiodynamics, Inc., Queensbury, N.Y., USA), which was initially used specifically for liver resections. Methods: A search using Medline, Embase and Google™ Scholar was performed for the period 2001 to August 2011. The references of the studies included were also reviewed. There was only one published series of distal pancreatectomies; these were laparoscopic and included 14 patients. The review of bipolar RF-assisted liver resections, partial nephrectomies and distal pancreatectomies reported in the literature to date shows that there are significant advantages in using this device in these types of operation [359].

Adrenalectomy

Indications and survival benefit for adrenalectomy (ADX) in the setting of metastasis are not clearly defined. We aimed to determine which patients with primary malignancies may benefit from ADX performed for metastasis. Mayo Clinic institutional outcomes in patients with

metastatic disease to the adrenal(s) treated by adrenalectomy were compared to stagematched historical controls from the Surveillance Epidemiology and End Results (SEER) database. A retrospective review (1992-2010) was conducted to identify patients treated with ADX for metastatic cancer. Associations of clinical, surgical, and pathologic features with overall survival (OS) were evaluated using Cox proportional regression models. OS for those treated with ADX was compared with that for SEER database stage-matched patients who underwent primary resection without resection of distant disease using log-rank tests. A total of 166 patients underwent ADX for metastatic primaries involving the kidney 60, lung 24, sarcoma 19, colon 15, pancreas 13, and other-35. Patients with sarcoma and kidney, lung, and pancreatic tumors who underwent ADX had better OS at 1, 2, and 3 years than did the SEER-matched controls. Respectively, the rates were for sarcoma (100, 93, 86 % vs 57, 36, 30 %), kidney (86, 80, 72 % vs 55, 37, 27 %), lung (91, 69, 52 % vs 52, 34, 25 %), and pancreas (79, 56, 45 % vs 33, 20, 12 %). Univariate analysis identified primary diagnosis <2 years before ADX, other distant site, pancreatic primary, palliative operation, and persistent disease as risk factors for death. It was concluded that an aggressive surgical approach results in improved OS in patients with metastatic disease arising from soft tissues, kidney, lung, and pancreas. Other tumors may benefit, but larger study cohorts are needed for a meaningful comparison [360].

Cancer of the body and tail

Presenting symptom

Large bowel obstruction with perforation is an anomalous presentation of pancreatic tail carcinoma. Pancreatic cancer is often difficult to diagnose clinically and is especially furtive when it is located in the tail of the pancreas. It was described a patient who presented with large bowel obstruction due to splenic flexure mass which proved to be due to pancreatic mucinous adenocarcinoma. Pancreatic adenocarcinoma can rarely have the same presentation as colon cancer, and should therefore be considered in the differential diagnosis of large bowel obstruction. Although large bowel obstructing mass often due to colon cancer, pancreatic adenocarcinoma can rarely have the same presentation, and should be considered in the differential diagnosis of large bowel obstruction. Patients with a known diagnosis of pancreatic cancer presenting with large bowel obstruction with hemodynamic stability are better served with colonic stenting to relief the obstruction as well as being a palliative measure. On the other hand, if they present with proximal colonic perforation, exploratory laparotomy with resection of perforated colon segment and end ostomy is sufficient. Extended resection for patients with known pancreatic cancer presenting with large bowel obstruction is not justified as it is non curative and is associated with a high incidence of morbidity and mortality. Fixation of an obstructing colon mass to the pancreas should raise concerns of pancreatic cancer as the source of the obstruction. Frozen section examination might be helpful in these circumstances to avoid unnecessary extensive resection [361].

Distal pancreatectomy

Distal pancreatectomy is indicated for lesions in the pancreatic body and tail. Understanding of the anatomical structure of the pancreas and its surroundings is required in various situations in left upper abdominal surgery including the laparoscopic approach. Spleen-preserving distal pancreatectomy is indicated for lesions confined to the pancreas. Two major spleen-preserving procedures reported are the Warshaw procedure that conserves the spleen by blood flow from the short gastric vessels and the Kimura procedure that preserves the spleen with splenic vessels. Considering the laparoscopic approach, the surgeon may preserve splenic vessels from the median toward the splenic hilum without mobilization of the spleen. A standard distal pancreatectomy using the medial approach is presented on video.

The intraoperative complications of distal pancreatectomy can be minimized by avoiding splenic capsule injury, by careful differentiation of the splenic artery from the common hepatic artery, and by secure closure of the splenic vein stump. The incidence of postoperative pancreatic fistula following distal pancreatectomy is reported to be 13 percent in a nationwide pancreatic cancer registry. Based on the results of an international randomized trial of hand-sewn and staple closure of the pancreatic stump, the closure method of the pancreatic stump can be the surgeon's choice [362].

Antegrade modular pancreatosplenectomy procedure

The radical antegrade modular pancreatosplenectomy (RAMPS) procedure is a modification of standard distal pancreatosplenectomy. It was designed to provide the operative approach developed for cancers of the head of the pancreas to cancers of the body and tail of the pancreas, particularly with respect to the extent of node dissection and emphasis on obtaining microscopically negative tangential margins. The purpose of this report is to provide long-term survival results. Forty-seven patients had RAMPS between 1999 and 2008. The decision to perform anterior vs posterior RAMPS was based on the position of the tumor as assessed by preoperative computed tomograms. Patients were entered in a prospective database and followed at intervals. Thirty-two patients had anterior RAMPS and 15 had posterior RAMPS. Twenty-four patients had resection of 33 organs in addition to the left adrenal gland in the posterior RAMPS. Specimens were inked in the operating room. Mean tumor size was 4.4 cm. Negative tangential margins were obtained in 89% of specimens. Overall, the R0 rate was 81 percent. Mean lymph node count was 18. There were no 30-day or in-hospital mortalities. Mean and median follow-up times of living patients were 44 and 26 months. Median survival was 26 months and 5-year overall actuarial survival was 36 percent. The actual survival of 23 patients whose surgery was performed more than 5 years before the time of analysis was 31 percent. It was concluded that RAMPS is associated with high negative tangential margin rates and very satisfactory survival rates for this aggressive tumor [363].

Appleby operation (including celiac axis)

The clinical impact of the distal pancreatectomy with en-bloc celiac axis resection for locally advanced pancreatic body cancer remains unclear. It was reviewed the records of 13 patients who underwent distal pancreatectomy-celiac axis resection between 1991 and 2009. 58 patients who underwent distal pancreatectomy for pancreatic body cancer involving major vessels, the extrapancreatic neural plexus or other organs (T4 according to the Japanese stage classification) between 1991 and 2009, and 24 patients with unresectable locally advanced pancreatic cancer without distant metastases (unresectable group) between 2001 and 2009. The clinicopathologic factors and overall survival among the 3 groups were compared. The distal pancreatectomy-celiac axis resection group was associated with a significantly higher incidence of morbidity (92 % vs 60 %) and positive surgical margins (69 % vs 26 %) than the distal pancreatectomy group; however, no survival difference was found between the 2 groups. No survivor has lived more than 3 years after operation in the distal pancreatectomy-celiac axis resection group. The distal pancreatectomy-celiac axis resection group had a significantly better prognosis than the unresectable group (median survival time, 21 vs 10 months). Aggressive resection for T4 pancreatic body cancer by distal pancreatectomy-celiac axis resection can be justified for otherwise unresectable tumors. The surgical indication should be evaluated carefully because of the higher incidence of morbidity and lower incidence of curability compared with distal pancreatectomy, as well as because there have been no long-term survivors so far [364].

A 68-year-old man with locally advanced pancreatic body cancer invading the celiac axis (including common hepatic artery) and in contact with the superior mesenteric artery (SMA)

underwent 2 courses of neoadjuvant chemotherapy; gemcitabine hydrochloride (GEM 1,000 mg/m², on day 1 and 15) and S-1 (100mg/m² day, 2-weeks of continuous administration followed by 1-week rest). The tumor volume and the contact area to SMA were greatly diminished. All tumor markers were reduced. He underwent R0 resection by distal pancreatectomy with en bloc celiac axis resection (DP-CAR). After the surgery, he could continue adjuvant chemotherapy; (GEM 1,000 mg/m²) only twice because of malnutrition. Nine months later CT revealed local recurrence and multiple lung metastases. The patient died 371 days after surgery. Appropriate neoadjuvant therapy can contribute to R0 resection in locally advanced pancreatic cancer [365].

Laparoscopic resection

The role of laparoscopic resection in patients with pancreatic cancer remains to be clarified, because previous reports have not clearly defined oncologic outcomes. The objective of the present study was to investigate this question with the rate of R0 resection and long-term survival as endpoints. One retrospective observational study included prospectively collected data from 40 patients operated laparoscopically with curative intent for exocrine pancreatic malignancies identified among 250 consecutive patients undergoing laparoscopic pancreatic operations since 1997. All 40 patients had histologically verified exocrine pancreatic carcinoma. Ten patients (25 %) with typical ductal adenocarcinoma of the pancreas were deemed nonresectable by laparoscopic staging. Laparoscopic distal pancreatectomy was performed in 29 patients; 8 resections were combined with resections of adjacent organs and 1 removal of a malignant intraductal papillary mucinous neoplasm what appeared to be ectopic pancreatic tissue. In 1 patient, the resection was completed by hand-assisted technique, and 1 procedure was converted to open resection. Postoperative morbidity was 23 percent (n=7). The median hospital stay was 5 days (range, 1-30). The rate of R0 resections was 93 percent. Postoperative 3-year survivals rates were 36 percent for the entire cohort (n=30) and 30 percent in typical ductal adenocarcinoma (n=21). Laparoscopic distal pancreatectomy for exocrine pancreatic carcinoma is thus comparable with outcomes after open surgery and supports the concept that laparoscopic distal pancreatectomy is a safe, oncologic procedure [366].

Laparoscopic distal pancreatectomy has become the gold standard for benign tumors. As more surgeons have expertise in open and laparoscopic pancreatic surgery, increasing numbers of benign-appearing tumors are being removed via minimally invasive techniques and found to have malignancy on final pathology. Because of our growing experience in laparoscopic distal pancreatectomy, we have begun removing preoperatively suspected malignancies in the distal pancreas with minimally invasive techniques. All cases were collected prospectively in a database and analyzed retrospectively. All cases begun laparoscopically with the intention of performing the resection with minimally invasive techniques were considered even if the operation was ultimately converted to an open procedure. A total of 12 cases have been attempted of which four required hand assistance and one required conversion to an open approach due to delayed bleeding from a calcified splenic artery that had been transected with laparoscopic GIA stapler device. In total, eight (67 %) patients had malignant disease and four (33 %) were found to have benign tumors. The median lymph node retrieval is 8 (range 3-16) with no positive margins. The morbidity rate is 17 percent with one reoperation (8%) and one mortality (8%) at 30 and 90 days. The laparoscopic approach to malignant pancreatic tumors is thus feasible with similar morbidity and mortality rates to benign series. When tumors are next to the confluence of the splenic portal vein, a hand-assisted approach may be adviseable. Calcified splenic arteries should be sought on preoperative imaging and either transected in non-calcified segments or controlled via open techniques via the hand port [367].

Laparoscopic distal pancreatic surgery has gained popularity in the last decade. However, well-designed studies comparing laparoscopic distal pancreatectomy (LDP) to open distal pancreatectomy (ODP) are limited. It was presented a single-institution case-control study comparing outcomes of LDP to ODP. From a prospectively accruing database, 104 patients who underwent distal pancreatectomy for pancreatic pathologies were eligible. Of these, 30 LDPs were matched with 30 ODPs using a 1:1 case-match design. Matching criteria were final histopathologic diagnosis and lesion size. Twelve LDPs were excluded from analysis because of lack of adequate ODP controls. In all cases, an attempt was made at conservation of the spleen. There were more females in the LDP group. Other clinicopathologic characteristics of the LDP and ODP groups such mean age, prior history of upper abdominal surgery or pancreatitis, histopathologic diagnosis, lesion size on imaging, and histopathology were comparable. There were no significant differences in postoperative complication rates (50 % vs 43 %), major complication rates (20 % vs 20 %), grade B/C pancreatic fistula rates (17 % vs 13 %), or reoperation rates (3.3 % vs 6.7 %) between LDP and ODP groups, respectively. There was a significantly higher rate of splenic conservation in the LDP group (70 % vs 30 %). The intraoperative blood loss (294 \pm 245 v. 726 \pm 709 ml) and mean duration of hospitalization $(8.7 \pm 4.2 \text{ vs } 12.6 \pm 8.7 \text{ days})$ were significantly lower in the LDP group compared to the ODP group. It was concluded that LDP is a safe and feasible option for distal pancreatic resections in experienced centers. The postoperative complication rate is comparable to that of ODP. LDP is associated with lower operative blood loss, higher rate of splenic conservation, and shorter duration of hospitalization. These encouraging results demand further validation in prospective randomized trials [368].

Spleen-preserving laparoscopic distal pancreatectomy

It was evaluated vascular patency and potential changes in preserved spleens after laparoscopic spleen-preserving distal pancreatectomy (SPDP) with conservation of both splenic vessels. It was retrospectively analyzed the patency of conserved splenic vessels in patients who underwent laparoscopic or robotic splenic vessel-conserving SPDP from 2006 to 2010. The patency of the conserved splenic vessels was evaluated by abdominal computed tomography and classified into three grades according to the degree of severity. Among 30 patients with splenic vessel-conserving laparoscopic SPDP, 29 patients with complete follow-up data were included in this study. During the follow-up period (median: 13 months), grades 1 and 2 splenic arterial obliteration were observed in one patient each. A total of five patients (17 %) showed grade 1 or 2 obliteration in conserved splenic veins. Most patients (83 %) had patent conserved splenic vein. Four patients (14 %) eventually developed collateral venous vessels around gastric fundus and reserved spleen, but no spleen infarction was found, and none presented clinical relevant symptoms, such as variceal bleeding. There was no statistical difference in vascular patency between the laparoscopic and robotic groups. Most patients showed intact vascular patency in conserved splenic vessels and no secondary changes in the preserved spleen after laparoscopic splenic vessel-conserving SPDP [369].

Laparoscopic spleen-preserving distal pancreatectomy can be performed with or without splenic vessels conservation. The formation of perigastric varices is the main long-term complication and represents the area of major concern among surgeons. Aim of one paper was to evaluate the outcomes of patients who underwent spleen-preserving distal pancreatectomy (with or without splenic vessels conservation) at our institution. A retrospective search of an electronic database from 1999 through 2007 was performed. Standard statistical methods were used. Fourty-three individuals were analyzed. Postoperative morbidity was 56 percent. Patients managed by splenic vessels conservation were 36; in the remaining seven splenic vessels resection was performed. Pathologic details and the rate postoperative complications were not different between the two groups. Two splenectomies were necessary for postoperative splenic infarction (one in each group). 28 patients accepted the follow-up protocol. At 12 months, the rate of perigastric varices was 60 percent after splenic vessels resection and 22 percent after splenic vessels conservation. No

gastrointestinal bleeding occurred at a median follow-up of 69 months (37-139). It was concluded that laparoscopic spleen-preserving distal pancreatectomy is feasible. A moderate risk of postoperative splenic infarction has to be taken into account, and the formation of perigastric varices may be interpreted as a paraphysiologic phenomenon, especially after splenic vessels resection [370].

Margins

The aims of one study were to clarify the type of intrapancreatic spread of cancer of the pancreatic body and tail and to assess whether a 2-cm transection margin is adequate to ensure negative margins. It was to selected 66 patients who underwent distal pancreatectomy for cancer of the pancreatic body and tail. It was investigated intrapancreatic cancer spread in these patients histopathologically and analyzed the relationship between 2-cm-margin positivity and other clinicopathological characteristics. Two-centimeter-margin positivity was observed in 17 cases. In these, tumors had a tendency to spread toward the pancreatic head along the main pancreatic duct. As a result of statistical analysis, it was considered venous invasion (odds ratio 15.5), 2-cm-margin fibrosis (OR 174), and 2-cm-margin hardness (OR, 6.0) as being independently related to 2-cm-margin positivity. The results suggest that 2 cm is not a safe length to ensure a negative margin. In the future, preoperative and intraoperative evaluation of the degree of fibrosis of pancreatic parenchyma could lead to cancer-free pancreatic cut-end margins [371].

Chyle leak

Recent studies have demonstrated the feasibility and safety of fast-track protocols and early enteral feeding in abdominal surgery. Early enteral feeding may be one of the most important steps in the fast-track protocols. Following the suggestion that early enteral support could be beneficial in reducing postoperative infectious complications and improving patient's outcome, it was modified and introduced a fast-track program to allow the early introduction of enteral nutrition after distal pancreatectomy (DP). It seemed to be during this period of early feeding that chyle leak became problematic in our institute. Postoperative chyle leak is a rare complication of abdominal surgery. There are few reports regarding the incidence of chyle leak in pancreatic surgery. These reports revealed that the incidence of chyle leak after pancreatic surgery was 2 to 13 percent. From 1995 to 2010 DP was performed on 138 patients. There were 59 cases of pancreatic cancer, 36 cases of intraductal papillary mucinous neoplasm or mucinous cystic neoplasm, and 43 cases of other conditions. The protocol of early enteral feeding and ambulation involved the use of a fasttrack program as introduced in January 2006. Over a 4-year period, 75 patients underwent DP (fasttrack group). Compared with the previous traditional pathway, changes involved earlier oral feeding including the removal of nasogastric tube on postoperative day 1, liquid drinks on day 2, and liquid feeding with 15 g fat from day 3. The traditional protocol included nasogastric decompression until day 2, liquid drinks from days 2 to 7 and solid food from days 3 to 14, drain removed or changed on postoperative days 7 to 14; no specific action on mobilization was defined. It was defined chyle leak as a drain output with obvious milky appearance concurrent with the start of enteral feeding, and improved immediately upon discontinuing enteral feeds. (Several cases measured drain fluid levels of triglyceride. All of those that contained milky nonpurulent fluid had triglyceride levels greater than 110 mg/dL.) The incidence of chyle leak was 8 percent (11/138) in all patients. The timing of start for enteral feeding was significantly earlier in the fast-track group (median, day 3) compared with the traditional group (median, day 5). Incidence of chyle leak was significantly increased in the fast-track group compared to the traditional group (13 % vs 2 %, respectively). In comparison of clinical features, there were no significant differences between the patients with chyle leak and those without chyle leak except for early enteral feeding. Five-day fast therapy with total parenteral nutrition was effective for all of our patients with chyle leak. No

patients required the use of somatostatin analogs. Chyle leak was one risk factor for prolonged hospital stay but could be successfully treated with dietary measures. Several authors suggest lymph node dissection, neoplastic diseases, and chronic pancreatitis as risk factors for the development of chyle leak. It has been suggested that the mechanism of action leading to chyle leak may be due to the lipid content of the enteral feed, which may keep the visceral lymphatic channels that have been divided as part of the standard resection open, thus leading to the persistent chyle leak.Chyle leak did occasionally occur despite a period of gut rest; however, it was during this period of early feeding that chyle leak became most problematic. This leads to the recognition that the likely source of this chyle was an early stimulation of the lymphatic drainage of the small intestine. The results suggest that the visceral lymphatic channels may have remained open at least until 4 days postoperatively because all of the patients with chyle leak were started on enteral feeds on day 3 or 4. There is little doubt that enteral nutrition carries advantages over total parenteral nutritional support. It is also easier to administer. There may be preservation of gut barrier function with enteral feeding, and it may prevent structural alterations induced by starvation and injury. However, several randomized controlled trials demonstrated that immediate postoperative enteral feeding through a jejunostomy tube is not beneficial in patients undergoing PD and is even associated with impaired respiratory mechanics and postoperative mobility [372].

Other postoperative complications

The method to lower postoperative pancreatic fistula (POPF) after distal pancreatectomy (DP) involves controlling risk factors for leakage from the pancreatic stump. In order to promote homogeneity, it was used a single surgeon case series and then calculated POPF with a public web-based tool based on the severity classification system of the International Study Group of Pancreatic Surgery (ISGPS). A total of 223 consecutive cases of DPs were reviewed. DP involved the same hand-sewn fish-mouth closure of the pancreatic stump. All received postoperative epidural anesthesia. Logistic regression analysis identified risk factors for clinically relevant POPF (grade B/C). Mortality was zero. ISGPS gradings were: no POPF 53 percent, grade A = 32 percent, B = 14 percent, and C = 1 percent. The clinicalrelevant POPF (B/C) rate was 15 percent of which 24 percent represented surgical drain failure due to lack of patency and/or misplaced from their original location. Preoperative endoscopic ablation and/or stenting of Wirsung's duct was a significant risk factor to lower grade B/C leak (3 %). Multivariate analysis identified two controllable risk factorsintraoperative blood loss >1,000 ml and those who did not undergo preoperative endoscopic interventions of Wirsung's duct. In the group with presumed intact pancreatic sphincters (no endoscopic intervention, n=177), the use of postoperative intravenous opioids (with epidural failure) was a risk factor for B/C leak (34 %). These findings suggest that increased back pressure in the pancreatic duct has a role in promoting pancreatic stump leakage. It was concluded that using the ISGPS definition and its web-based tool, the incidence of clinically relevant leakage was 15 percent in 223 cases of DP. Opportunities to lower this rate are improving the surgical drain technology, limiting intraoperative blood loss, and avoiding postoperative intravenous narcotics with epidural analgesia [373].

Survival

Patients with pancreatic adenocarcinoma have poor survival. Presumably, tumors in the body or tail of the pancreas, due to paucity of symptoms, present later than patients with tumors in the head of the pancreas. One study was undertaken to determine if tumors amenable to complete extirpation by distal pancreatectomy/splenectomy have worse survival when compared to their proximal counterparts. Since 1992, patients undergoing pancreatico-duodenectomy or distal pancreatectomy/splenectomy for pancreatic adenocarcinoma have been prospectively followed. Two hundred twenty patients underwent pancreaticoduoden-

ectomy and 33 patients underwent distal pancreatectomy/splenectomy for pancreatic adenocarcinoma. Comparing overall survival, there was not a significant difference between patients undergoing pancreaticoduodenectomy (17 months, 26 ± 26) and distal pancreatectomy/splenectomy (15 months, 20 ± 19). Patients undergoing distal pancreatectomy/splenectomy had significantly larger tumors (4 cm, 5 ± 2) compared to patients undergoing pancreaticoduodenectomy (3 cm, 3 ± 1). It was concluded that long-term survival after resection of pancreatic adenocarcinoma is poor despite the location within the pancreas. Complete tumor extirpation continues to be an independent predictor of survival, regardless of operation undertaken, despite larger tumors for patients who undergo distal pancreatectomy/splenectomy [374]

Postoperative care

Physical training

As patients with pancreas and periampullary cancer (PPC) experience improved survival rates and longevity, the focus shifts toward living life while surviving cancer. Fatigue is the most commonly reported symptom in all cancer patients. Exercise has been found to effectively decrease fatigue levels and improve physical functioning in cancer patients. One hundred two patients with resected PPC consented to participate in this study and were randomized to either an intervention group (IG) or a usual care group (UCG). Subjects completed visual analog scales, the FACIT-Fatigue Scale and the Short Form-36v2 after surgery and again 3 to 6 months after hospital discharge. Patients in the IG and UCG were comparable with regard to demographics, comorbidities, cancer type and staging, type of resection, preoperative fatigue and pain levels, adjuvant therapy, and baseline walking distance. Patients in the IG had significantly improved scores on the FACIT-Fatigue Scale at study completion, improved fatigue and pain scores, as well as overall physical functioning and mental health composite scores. At study completion, participants in the IG were walking twice as far and were significantly more likely to have continued walking or another form of exercise as compared with the UCG. Using hierarchical cluster analysis, 3 mutually exclusive symptom groupings were identified in the cohort. Kaplan-Meier survival analysis did not indicate an overall survival benefit for the IG. This first prospective, randomized controlled trial report that participation in a home walking program confers a significant benefit in resected PPC patients with regard to fatigue levels, physical functioning, and health-related quality of life [375].

Discharge after pancreatic resection

The aim of one study was to analyse national trends in discharge disposition following pancreatic resection for malignancy in the USA. The Nationwide Inpatient Sample database was queried for 1993-2005 to identify patients who underwent pancreatic resection for malignancy. The status of patients at discharge (to home, home with home health care or to another facility) was noted. A weighted total of 51 866 patients who underwent pancreatectomy for malignant neoplasm of the pancreas were identified. Patients who died in the postoperative period and patients without a specified discharge disposition were excluded, leaving 43 603 patients for inclusion in the study. Overall mortality improved over the period of the study from 7.1 percent in 1993 to 5.2 percent in 2005. The number of patients discharged to another facility increased significantly from 6 percent in 1993 to 13 percent in 2005. Similarly, the number of patients discharged to home with home health assistance increased from 20 percent in 1993 to 33 percent in 2005. This corresponded with a statistically significant decrease in the number of patients discharged to home without assistance, from 75 percent in 1993 to 54 percent in 2005. The results of the study

demonstrate that following pancreatic resection for malignancy, nearly half the patients will require some assistance after discharge [376].

Postoperative complications

Post-pancreatectomy bleeding

Although postpancreatectomy hemorrhage (PPH) is observed infrequently after pancreatic surgery, it remains a serious complication with a high rate of mortality. Recently, the International Study Group of Pancreatic Surgery (ISGPS) issued a new definition for PPH. A weak point of the new PPH grading system is the definition of grade A bleeding that subsumes mild bleedings within the first 24 as "small or medium volume blood loss (drop of hemoglobin concentration of <3 g/dL) with no or minimal clinical impairment, no need for invasive intervention, and successful conservative treatment." Treatment of patients after operation on intensive care unit may also cause a decrease in Hb levels, resulting in falsepositive classifications. To evaluate and validate this new definition, it was analyzed data retrospectively from 945 patients who underwent pancreatic surgery between 1993 and 2009 were identified retrospectively from a prospective database with regard to the occurrences of PPH. It was graded the hemorrhages recorded in the database according to the ISGPS consensus definition. It was assessed the clinical course, morbidity, mortality, and duration of hospital stay for patients with grade B and C PPHs in comparison with patients who underwent pancreatic resections without hemorrhage. Grade B PPH after pancreatic surgery occurred in 16 patients (1.7 %), and grade C PPH occurred in 38 patients (4.0 %). In the study, patients with grade B PPH had greater incidences of intraluminal bleeding, and grade C PPH patients exhibited greater occurrences of extraluminal bleeding. Early extraluminal bleeding in grade B patients was often the result of inadequate hemostasis at the time of operation. Bleeding in this location is relatively easy to manage and has a relatively low mortality rate. Extraluminal bleeding in grade C patients correlated with anastomotic leaks at the bilio- and pancreatico-enteric anastomoses and were located mainly in the retroperitoneal operative field or peripancreatic vessels. Grade C intraluminal bleedings usually occurred from the pancreatic parenchyma at the site of gland transaction. Contrary to PPH that occurred early postoperatively (first 24 hours), these types of PPH, particularly extraluminal bleeding, are much more difficult to handle because of the underlying pathogenesis and have greater mortality rates. The aggressive therapeutic efforts required to treat these PPH are mirrored by the associated morbidity. Although 7 percent of patients without PPH underwent relaparotomy, 38 percent of patients with grade B PPH and 74 percent of patients with grade C PPH required relaparotomy, this difference was statistically significant. Indeed, nearly all types of complications were more common in patients with grades B and C PPH. One of the most important findings was that PPH contributed to nearly one-half of the mortality. In the analyzed patient cohort, PPH accounted for 14 of the 32 postoperative deaths in all 945 patients. This mortality demonstrates the clinical severity of PPH. The duration of ICU stay can also be used as a measure of the morbidity associated with the postoperative course. In the present study, the median duration of the postoperative ICU stay was significantly prolonged in patients with PPH. Follow-up of the patients revealed that PPH also impairs the health of the patients in lifelong terms. None of the patients with grade B PPH reported rehospitalization. In contrast, 21 percent of the patients with grade C PPH reported rehospitalization as the result of abdominal pain, infections, endocrine insufficiency, and renal insufficiency. Of the latter group, 36 percent of the patients also reported subjective impairment in quality of life as the result of intraabdominal pain. Morbidity was also increased in patients with grade B (77 %) and C (95 %) PPH compared with control patients (60 %). Grade B and C PPH correlated significantly with the incidence of grade C postoperative pancreatic fistula (15 % vs 2 %), grade C delayed gastric emptying (19 % vs 4 %), and wound infection (39 % vs 14 %) compared with control patients. The data

indicate that the new definition correlates well with morbidity, mortality, and duration of hospital stay. The definition, therefore, seems suitable for clinical and scientific applications [377].

Pancreatic fistula

MRI

Pancreatic fistula (PF) is considered to be the main cause of morbidity after pancreaticoduodenectomy (PD). A recent study from our institution suggested the risk for pancreatic fistula after distal pancreatectomy to be closely related to the pancreatic remnant volume (PRV). The hypothesis was formulated that after PD the PRV is an important determinant of the risk for PF formation. All patients undergoing PD between 2007 and 2010 were included. Preoperative multidetector computed tomography (CT) or magnetic resonance imaging (MRI) was used to calculate the PRV and the pancreatic duct width (PDW) at the alleged resection line. A total of 182 patients (median age 67 years) undergoing PD were included. The diagnosis was malignant in 144 patients (79%) and benign in 38 (21%). Pancreatic fistula defined according to the International Study Group on Pancreatic Fistula (ISGPF) criteria was diagnosed in 37 patients (20 %). The median PRV was 35 cm³ and the median PDW was 4 mm. In a univariate analysis a large calculated volume of the pancreatic remnant increased the subsequent risk of PF (odds ratio, OR, 3.7; 95 % confidence interval 1.6 to 8.7), as did a small duct width (OR, 8.5; 95 % confidence interval 3.1 to 23.0). According to the multivariate analysis, the size of the pancreatic remnant and the width of the pancreatic duct maintained their impact on leakage risk. A large pancreatic volume and small pancreatic duct increase the risk of PF. Preoperative CT and/or MRI therefore are useful in predicting fistula formation before pancreaticoduodenectomy [378].

Body mass index

Pancreatic fistula (PF) after pancreaticoduodenectomy (PD) is still a severe complication and a challenging problem. The common risk factors are the soft pancreas and small pancreatic duct of the remnant pancreas. Those two risk factors were recognized during surgery. On the other hand, a preoperatively determined risk factor of PF is unclarified. It was conducted a retrospective analysis of 203 patients consecutively treated by PD from 2000 to 2010. PF was defined according to the criteria of the International Study Group of Pancreatic Fistula. Clinical and pre- and intraoperative data were compared between PF and non-PF patients. The recommended cutoff value of body mass index (BMI) as 20 kg/m² was defined by receiver operating characteristic curve analysis. PF occurred in 53 (26 %) of 203 patients. In univariate analysis, BMI and soft pancreas were also risk factors of PF. Patients with PF had a significantly longer hospital stay than non-PF patients. High BMI and soft pancreas were significant risk factors for PF [379].

Staplers

Pancreatic fistula continues to be a source of significant morbidity following distal pancreatic resections. The technique of pancreatic division varies widely among surgeons, and there is no evidence that identifies a single method as superior. In our practice, the technique of distal pancreatic resection has evolved from cut-and-sew to stapled technique with green and recently white cartridge. The aim of our study was to evaluate the rate of clinically significant fistulas (International Study Group on Pancreatic Fistula (ISGPF) grade B or C) following distal pancreatectomy and to identify variables associated with a low rate of fistula development. Clinical records of all patients who underwent distal pancreatic resections between February 1999 and July 2010 by a single surgeon were retrospectively reviewed focusing on the incidence and type of pancreatic fistula as defined by ISGPF. Study variables included age, gender, surgical approach, extent of resection, ASA classification, type of

stapler cartridge, use of Seamguard[™], and ISGPF classification. Statistical analysis was performed using Fisher's exact test, and univariate and multivariate logistic regression. Sixtyfour patients (median age 60, range 21-85; 54 % male) underwent distal pancreatic resection (laparoscopy 50 % vs open 50 %). The most common indications were pancreatic adenocarcinoma (n=15; 23 %) and neuroendocrine neoplasms (n=14; 22 %). Clinically significant pancreatic fistula developed in 24 percent (n=15). The rate of fistula with cut-andsew technique was 36 percent (4/11), with stapled green cartridge 31 percent (9/29) and only 5 percent (1/21) with stapled vascular cartridge. Univariate logistic regression identified vascular cartridge size (OR 0.11) and open stapled technique (OR 0.12) as variables significantly associated with a low fistula rate. Both vascular cartridge size (OR 0.10) and open stapled technique (OR 0.08) remained significant when analyzed by multivariate logistic regression. Division of pancreatic parenchyma with vascular cartridges resulted in significantly (OR 9.0) lower fistula rate compared to green cartridges. The use of Seamguard[™] did not affect fistula rate (16 % vs 27 %) nor did the performance of multivisceral resection vs. distal pancreatectomy/splenectomy alone (21 % vs 23 %). It was concluded that the optimal technique of pancreatic division has not been conclusively established. Dividing the pancreas utilizing vascular (2.5 mm) staple cartridges significantly decreased the rate of clinically significant pancreatic fistula and it has changed our practice accordingly. A prospective randomized trial is necessary to validate these results [380].

Prevention (omental roll-up technique)

Most morbidity and mortality are caused by a pancreatic fistula after pancreaticoduodenectomy (PD), and its prevention is the major concern. It was applied the omental roll-up technique around pancreaticojejunostomy and investigated the effectiveness of this technique to prevent a pancreatic fistula. Between 2009 and 2011, 68 patients underwent PD. The patients were divided into 2 groups according to the surgical application of the omental roll-up technique around the PJ site: group 1 (those who did not undergo the omental roll-up technique) compared with group 2 (those who did undergo the omental rollup technique). No differences were noted in the clinical characteristics, including patients' demographics and operation-related factors, between the 2 groups. A pancreatic fistula occurred in 23 of 39 patients in group 1 (59 %) and in 6 of 29 patients in group 2 (21 %). Group 2 had a significantly lower incidence of pancreatic fistula, and these fistulas were classified as being grade A using the International Study Group on Pancreatic Fistula Definition showing a transient high amylase level in the drainage fluid without significantly affecting the patient's recovery. Drain removal was performed earlier in group 2. Mean postoperative hospital stay was 23 days in group 1 compared with 16 days in group 2. Overall mortality was 1.5 percent; however, no deaths were related to a pancreatic fistula. It was concluded that the omental roll-up technique for the PJ site definitely reduced the occurrence of a pancreatic fistula. Therefore, the omental roll-up technique is a simple and effective strategy to prevent a pancreatic fistula [381].

Wrapping

Wrapping is thought to prevent pancreatic fistula and postoperative hemorrhage for pancreaticoduodenectomy (PD), and we analyzed whether omentum/falciform ligament wrapping decreases postoperative complications after PD. It was presented a retrospective study of wrapping using the omentum/falciform ligament in patients that underwent PD between 2006 and 2008 in 139 institutions that were members of the Japanese Society of Pancreatic Surgery. Ninety-one institutions responded to the questionnaires, and data were accumulated from 3,288 patients. The data from 2,597 patients were acceptable for analysis; 918 (35 %) patients underwent wrapping and 1,679 patients did not. A pancreatic fistula occurred in 623 patients (37 %) in the nonwrapping group, in comparison to 393 patients (43 %) in the wrapping group. The incidence of a grade B/C pancreatic fistula was lower in the nonwrapping group than the wrapping group (17 % vs 22 %). An intra-abdominal hemorrhage occurred in 54 patients (3.2 %) in the nonwrapping group, which was similar to the incidence in the wrapping group (32 patients; 3.5 %). The mortality was 1.3 percent and

1.0 percent in nonwrapping and wrapping groups, respectively. A multivariate analysis revealed 7 independent risk factors for pancreatic fistula; male, hypoalbuminemia, soft pancreas, long operation time, extended resection, pylorus preservation, and omentum wrapping. There were 4 independent risk factors for early intra-abdominal hemorrhage and 2 independent risk factors for late intra-abdominal hemorrhage. This retrospective study revealed that omentum wrapping did not decrease the incidence of pancreatic fistula. An additional validation study is necessary to evaluate the efficacy of wrapping for PD [382].

Fistulography

To evaluate the usefulness of fistulography as a diagnostic and management tool for clinically suspected pancreatic fistulas (PF) after pancreaticoduodenectomy (PD) 84 consecutive fistulographies were performed for clinical suspicion of PF and retrospectively analysed. It was radiologically defined two types of PF by means of fistulography, PF1 in the case of primary filling with contrast agent of the jejunal loop or stomach and PF2 in the case of secondary filling of the jejunal loop or stomach through a fistulous tract or a fluid collection. In 35/84 (42 %) of the fistulograms, a PF1 was demonstrated owing to an instantaneous opacification of the intestinal lumen or the stomach, without evidence of a fistulous tract or fluid collection. In 49/84 (58 %) fistulograms, a PF2 was demonstrated by the depiction of a fluid collection and/or a fistulous tract and a communication with the intestinal loop or the stomach anastomised with the pancreas. The mean healing time of a PF after PD was 3 days for PF1, and 10 days for PF2. Fistulography helps in the confirmation of clinically suspect PF, and can distinguish PF1 and PF2, thus decreasing post-operative morbidity significantly [383].

EUS-guided drainage

Endoscopic ultrasound (EUS)-guided drainage is widely used to manage pancreatic pseudocysts. Several studies have reported the use of EUS-guided drainage for pancreatic fistula and stasis of pancreatic juice caused by stricture of the pancreatic duct after pancreatic resection. At the authors' hospital, 262 patients underwent surgery involving pancreatic resection from 2005 to 2010. In 90 of these patients (34 %), a grade B or C postoperative pancreatic fistula developed that required additional treatment. The authors performed EUS-guided transmural drainage (EUS-TD) for six patients (2 %) with a pancreatic fistula or dilation of the main pancreatic duct visible by EUS. Percutaneous drainage was provided for 18 patients (7 %). The success rates for EUS-TD and percutaneous drainage were compared in a retrospective analysis. In all six cases, EUS-TD was performed successfully without complications. Five of the six patients were successfully treated with only one trial of EUS-TD. The final technical success rate was 100 percent for both EUS-TD and percutaneous drainage. Both the short- and long-term clinical success rates for EUS-TD were 100 percent and those for percutaneous drainage were 61 and 83 percent, respectively. The differences in these rates were not significant (short-term success vs long-term success). However, the time to clinical success was significantly shorter with EUS-TD (5.8 days) than with percutaneous drainage (30 days) in the current series. The EUS-TD approach appears to be a safe and technically feasible alternative to percutaneous drainage and may be considered as first-line therapy for pancreatic fistulas visible by EUS [384].

Urine trypsinogen 2

Previous reports suggested that the urine trypsinogen 2 (U-TRP2) test might be a valuable method for the diagnosis of postoperative pancreatitis after pancreatic surgery. It was hypothesize that the elevation of U-TRP2 level after pancreaticoduodenectomy (PD) could be associated with the occurrence of postoperative pancreatic fistula (POPF). A total of 130 consecutive patients undergoing PD with duct-to-mucosa pancreaticogastrostomy were included. Urine samples for evaluation of U-TRP2 levels were collected prospectively. Risk factors for POPF were evaluated using univariate and multivariate analyses. Of 130 patients, 19 developed POPF; grade A in 14 (11 %), grade B in 3 (2 %), and grade C in 1 (1 %).

Univariate analysis demonstrated that a nonobstructed main pancreatic duct, a pancreatic duct less than 3 mm, soft texture of the pancreatic gland, a PD with antrectomy, PD with hepatic resection, hyperamylasemia, and elevation of U-TRP2 levels (>50 μ g/L) were significantly associated with POPF. By multivariate analysis, elevation of U-TRP2 levels was the only independent risk factor that correlated with POPF. Elevation of U-TRP2 level is an independent risk factor for POPF after PD. Elevated U-TRP2 level might be the consequence of the postoperative pancreatitis, and postoperative pancreatitis may play an important role in the pathogenic mechanism of POPF after PD [385].

Prognostic factors

Japanese registry

Since 1981, the Japan Pancreas Society has been hosting a nationwide pancreatic cancer registry. To commemorate its 30th anniversary, it was review its history and latest achievement. During 3 decades, more than 350 leading institutions in Japan contributed voluntarily to register and periodic follow-up. The registry was modified to protect privacy by encrypting and hash algorithm. From 1981 to 2007, 32,619 cumulative records were analyzed. The overall survival of invasive cancer was improved significantly. More patients with earlier stage or with intraductal and cystic neoplasms underwent resection. The strongest prognostic factor of Union for International Cancer Control (UICC) stage IIA and IIB tubular adenocarcinoma in the pancreatic head was histological grade, followed by tumor size, extent of lymph node dissection, and postoperative chemotherapy. The 5-year survival rate of Union for International Cancer Control stage 0 reached 85 percent. The improvement of survival of patients with invasive cancer in Japan can be attributed to the introduction of effective chemotherapies, regionalization, and the earlier diagnosis and treatment. Simple definition of "early pancreatic cancer" is needed [386].

Metastatic lymph node ratio

Overall five year survival following pancreaticoduodenectomy for ductal adenocarcinoma is poor with typical reported rates in the literature of 8-27 percent. The aim of one study was to identify the histological variables best able to predict long-term survival in these patients. A prospective database of patients undergoing pancreaticoduodenectomy between 2002 and 2009 was analysed to identify patients with histologically proven pancreatic ductal adenocarcinoma. Patients with ampullary tumours, cholangiocarcinoma, duodenal adenocarcinoma and neuroendocrine tumours were excluded. The histology reports for these patients were reviewed. Uni-variate and multi-variate survival analysis was performed to identify variables useful in predicting long-term outcome. 134 patients underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma during this period. Five year survival in this series was 19 percent. Uni-variate analysis identified nodal status and the metastatic to resected lymph node ratio as predictors of survival. Using multi-variate Cox Regression analysis a metastatic to lymph node ratio of >15 percent and the presence of perineural invasion were identified as independent predictors of patient survival. Metastatic to resected lymph node ratio is better able to stratify prognosis than nodal status alone with 5 year survival of those with N0 disease being 56 percent and 13 percent for N1 disease. However for those with <15 percent of resected nodes positive, 5 year survival was 22 percent and in those with >15 percent nodes positive it was 5 percent. The metastatic to resected lymph node ratio can provide significant prognostic information in those patients with node positive disease after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma [387].

Perineural invation

Perineural invasion (PNI) is one of the established prognostic factors in pancreatic ductal adenocarcinoma (PDAC). However, the prognostic significance of PNI in patients with PDAC who received neoadjuvant therapy and pancreaticoduodenectomy is not clear. In one study, it was performed a detailed examination of neural invasion in pancreaticoduodenectomy specimens from 212 patients with PDAC who received neoadjuvant chemoradiation (treated group) and in 60 untreated patients at our institution between 1999 and 2007. The frequency of PNI was higher in the untreated group (80 %, 48/60) than in the treated group (58 %, 123/212). For the 123 treated cases that were positive for PNI. extratumoral PNI. intratumoral PNI, intrapancreatic PNI only, extrapancreatic PNI, and intraneural invasion were identified in 86 (70 %), 37 (30 %), 11 (10 %), 112 (91 %), and 35 cases (29 %), respectively. The presence of PNI correlated with tumor size, margin status, lymph node metastasis, pathologic tumor, and American Joint Committee on Cancer stages in the treated group. Tumor involvement of nerves >0.8 mm correlated with higher frequency of positive margin compared with tumors with PNI involving nerves ≤0.8 mm but not with other clinicopathologic parameters and survival. In the treated group, the presence of PNI or intraneural invasion correlated significantly with shorter disease-free survival and overall survival compared with no PNI or PNI only, respectively. PNI was an independent prognostic factor for both disease-free survival and overall survival in multivariate analysis. Our results showed that PNI plays an important role in the progression of PDAC and in predicting prognosis in this group of patients [388].

Although vascular invasion is a well-established indicator of poor prognosis for patients with infiltrating ductal adenocarcinoma of the pancreas (PDAC), the histopathologic characteristics of vascular invasion are not well described. Hematoxylin and eosin-stained slides from 209 surgically resected infiltrating PDACs were systematically evaluated for the presence or absence of microscopic vascular invasion. For the cases with vascular invasion, we further categorized the histologic pattern of invasion into conventional and pancreatic intraepithelial neoplasia-like (PanIN-like). In addition, several histopathologic factors in the surrounding blood vessels, including lymphocytic infiltration and luminal fibrosis, were carefully assessed. Data were compared with clinicopathologic variables, including patient survival. Microscopic vascular invasion was observed in 136 of the 209 PDACs (65 %). Vascular invasion mimicking pancreatic intraepithelial neoplasia (PanIN-like invasion) was observed in 94 of the 136 cases (69 %) with vascular invasion. Microscopic vascular invasion was associated with increased tumor size, higher pT classification, lymph node metastasis, and perineural invasion. Vascular invasion was inversely correlated with neo-adjuvant therapy. Examination of adjacent blood vessels revealed that peritumoral blood vessels with intimal lymphocytes, intimal and medial fibrosis, and cancer cells in vascular wall were all highly associated with the intraluminal vascular invasion. In univariate analysis, patients whose cancers had microscopic vascular invasion (median survival, 15 months) had a significantly worse survival than did patients with carcinomas without vascular invasion (25 months). Microscopic vascular invasion is a poor prognostic indicator and can histologically mimic PanIN [389].

Peritumoral lymphatic vessel density

Lymphatic vessels in primary tumor tissue play an important role in lymphatic metastasis. Lymphatic metastasis of malignant neoplasms is significantly related to prognosis, influencing both recurrence and survival. The aim of one study was to investigate the correlation of intra-tumoral lymphatic vessel density (iLVD) and peri-tumoral lymphatic vessel density (pLVD) with biological behavior and prognostic parameters in pancreatic carcinoma (PC) and other pancreatic tumors. Lymphangiogenesis was examined using the D2-40 monoclonal antibody in 33 cases of PC, 7 neuroendocrine tumors of the pancreas (NETP), 7

solid pseudopapillary tumors of the pancreas (SPTP) and 3 cystadenomas of the pancreas (CP). Positively-stained microvessels were counted at magnification x400 in dense lymphatic vascular foci (hotspots). The LVD of PC was compared to 3 other pancreatic tumors. The relationships among the LVD, the extent of differentiation, lymphatic invasion, lymph node metastasis and other clinicopathological parameters of PC were analyzed. There was no difference in the iLVD among PC, NETP, SPTP and CP. The pLVD of NETP was markedly higher than that of PC, SPTP and CP. The pLVD of PC was significantly higher than that of SPTP and CP, but there was no difference between SPTP and CP. The pLVD of PC was significantly associated with the extent of differentiation, lymphatic invasion and lymph node metastasis, whereas it was not associated with age, gender, tumor size, tumor location and peri-pancreatic invasion. The iLVD of PC was not correlated with these clinicopathological parameters. There was no difference in iLVD and no marked difference in pLVD among the pancreatic tumors, as pLVD can be utilized for the prediction of lymph node metastasis, thus aiding in the evaluation of patient prognosis [390].

Lymphovascular invasion

Lymphovascular invasion (LVI) is a prognostic factor in many types of human malignancies, including pancreatic ductal adenocarcinoma (PDAC). However, the prognostic significance of LVI in patients with PDAC who have received neoadjuvant therapy and pancreaticoduodenectomy is unclear. In one study, it was analyzed LVI in 212 patients who had received neoadjuvant chemoradiation and subsequent pancreaticoduodenectomy at our institution between 1999 and 2007. LVI was present in 62 percent (131/212) of the patients. Of the 131 patients who were positive for LVI, 67 (32 %) had tumor invasion into lymphovascular spaces without muscle layer (nonmuscular lymphovascular spaces), and 64 (30 %) had tumor invasion into muscular vessels. Tumor invasion into muscular vessels correlated with higher frequencies of positive resection margin, lymph node metastasis, and locoregional/distant recurrence. Patients with tumor invasion into muscular vessels had significantly shorter disease-free survival and overall survival than did patients who had no LVI or who had tumor invasion of nonmuscular lymphovascular spaces. Tumor invasion into muscular vessels is an independent prognostic factor in patients with PDAC who have received neoadjuvant therapies. The results showed that tumor invasion into muscular vessels play an important role in the progression of PDAC and in predicting prognosis in this group of patients [391].

Uncinate process pancreatic cancer

The objective of the study was to delineate surgical outcomes of pancreatoduodenectomy following neoadjuvant concurrent chemoradiation therapy (CCRT) in uncinate process pancreatic cancer (UPC). It was reviewed 97 patients with resected usual pancreatic head cancer (PHC) and UPC and analyzed clinicopathologic characteristics and survival outcomes of PHC and UPC with a review of the reported literature regarding UPC. Twenty-five patients (28 %) had UPC, and 72 patients had PHC. Pylorus-preserving pancreatoduodenectomy was performed in 67 patients (69 %) and conventional pancreatoduodenectomy in 28 patients (29 %), and 2 patients needed total pancreatectomies. When comparing UPCs with PHCs, less frequent jaundice and more advanced stages of cancers at the time of diagnosis (linear-to-linear association) were found in UPCs, and CCRT was administered more frequently in UPCs. Survival outcomes between PHC and UPC were similar, with median survival rates of 25.9 and 30.5 months, respectively. In addition, disease-free survival was similar between the 2 groups (16 and 15 months, respectively). The oncologic outcome of pancreatectomy for UPC is likely to be more acceptable compared with those previously reported in the literature. In conclusion, although UPCs are found in relatively advanced clinical stages, favorable oncologic outcomes may be obtained by pancreatectomy following preoperative CCRT [392].

Lymph node metastases in relation to cancer from ventral versus dorsal anlage

Pancreaticoduodenectomy is performed for pancreatic head cancer that originated from the dorsal or ventral primordium. Although the extent of lymph node (LN) dissection is the same irrespective of the origin, the lymphatic continuities may differ between the 2 primordia. Between 2003 and 2010, 152 patients underwent pancreaticoduodenectomy for pancreatic cancer. One hundred six patients were assigned into 2 groups according to tumor location on preoperative computed tomography, and their clinical and pathological features were retrospectively analyzed in view of the embryonic development of the pancreas. Sixty of 106 patients were classified with tumors that were derived from the dorsal pancreas (D group) and 46 from the ventral pancreas (V group). The frequency of LN involvement around the middle colic artery (LN 15) in the D group was significantly higher than in the V group. The rate of additional resection of the pancreas tended to be higher in the D group. The present study thus showed the detailed pattern of spread of pancreatic ductal carcinoma to the LNs and provided important information for determining the optimal surgical strategy [393].

Postoperative hepatic steatosis

The occurrence of hepatic steatosis after pancreatectomy has been previously known. However, this condition has been neglected because its clinical course has been considered benign. The aims of one study were to identify the risk factors for hepatic steatosis after pancreatectomy, to clarify the impact of this condition on long-term prognosis, and to suggest methods for preventing hepatic steatosis. One hundred two patients, who were diagnosed with postoperative computed tomography, were enrolled. The severity of hepatic steatosis was determined by using unenhanced computed tomography. The variables that might influence the development of hepatic steatosis were compared between the groups with and without hepatic steatosis. The incidence of postoperative hepatic steatosis was 31 percent. Multivariate analysis showed that absence of postoperative insulin use and decrease in postoperative body mass index of greater than 3 kg/m² were independent risk factors for hepatic steatosis. The cumulative recurrence-free survival rate of the group with hepatic steatosis was poorer than that of the group without. Thus, postoperative hepatic steatosis may affect long-term prognosis after pancreatectomy. Surgeons should take care of nutritional management including insulin therapy for patients with hepatic steatosis after pancreatectomy [394].

Age

To compare outcomes and the use of multimodality therapy in young and elderly people with pancreatic cancer undergoing surgical resection a retrospective, single-institution study was performed. Two hundred three individuals who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma comprised the study population. Participants were divided into three groups based on age (<65, n=97; 65-74, n=74; ≥75, n=32). Perioperative outcomes, the use of multimodality therapy, and overall survival of the different age groups were compared. Similar rates of perioperative mortality and morbidity were observed in all age groups, but elderly adults were more likely to be discharged to a rehabilitation or skilled nursing facility. A similar proportion of participants received neoadjuvant therapy, but a smaller proportion of elderly participants received adjuvant therapy. Overall survival was similar between the age groups. Predictors of poorer overall survival included coronary artery disease, positive resection margin, and less-differentiated tumor histology. Treatment with neoadjuvant and adjuvant therapy was predictors of better overall survival. It was concluded that carefully selected elderly individuals experience similar perioperative outcomes and overall survival to those of younger individuals after resection of pancreatic cancer. There appears to be a significant disparity in the use of adjuvant therapy between young and elderly individuals [395].

Scores

The objective of this study was to perform an external validation of 2 Asian prognostic indices for patients with advanced pancreatic cancer. A score was calculated in patients treated with frontline therapy derived from the factors Eastern Cooperative Oncology Group Performance Status, localization of primary tumor, and C-reactive protein level according to Sawaki and from the factors Eastern Cooperative Oncology Group Performance Status, pretreatment carcinoembryonic antigen, and presence/absence of distant metastasis following Ishii. For analysis, the Kaplan-Meier method and the log-rank test were used. An analysis of the Brier score was performed to determine how the prediction error was reduced by the introduction of prognostic factors. For the Sawaki and Ishii score, 112 and 105 complete cases were available, respectively. Based on the 3 prognostic categories according to the Sawaki score. median overall survival was 12, 10, and 6 months, respectively (not statistically significant). By adapting the Ishii score to our population, 93 percent of the patients were allocated to the subgroup with "good" and only 7 percent to the subgroup with "intermediate" prognosis. Corresponding median OS was 11 and 4 months, respectively. Both Asian indices may not be suitable for defining different prognostic subgroups for a white population with advanced pancreatic cancer [396].

Adrenalectomy

Indications and survival benefit for adrenalectomy (ADX) in the setting of metastasis are not clearly defined. It was aimed to determine which patients with primary malignancies may benefit from ADX performed for metastasis. Mayo Clinic institutional outcomes in patients with metastatic disease to the adrenal(s) treated by adrenalectomy were compared to stagematched historical controls from the Surveillance Epidemiology and End Results (SEER) database. A retrospective review (1992-2010) was conducted to identify patients treated with ADX for metastatic cancer at Mayo Clinic, Rochester. Associations of clinical, surgical, and pathologic features with overall survival (OS) were evaluated using Cox proportional regression models. OS for those treated with ADX was compared with that for SEER database stage-matched patients who underwent primary resection without resection of distant disease using log-rank tests. A total of 166 patients underwent ADX for metastatic primaries involving the kidney (n=60), lung (n=24), sarcoma (n=19), colon (n=15), pancreas (n=13), and others (n=35). Patients with sarcoma and kidney, lung, and pancreatic tumors who underwent ADX had better OS at 1, 2, and 3 years than did the SEER-matched controls, for pancreas (79, 56, and 45 % vs 33, 20, and 12 %). Univariate analysis identified primary diagnosis <2 years before ADX, other distant site, pancreatic primary, palliative operation, and persistent disease as risk factors for death. It was concluded that an aggressive surgical approach results in improved OS in patients with metastatic disease arising from soft tissues, kidney, lung, and pancreas. Other tumors may benefit, but larger study cohorts are needed for a meaningful comparison [397].

Microvessel density in lymph node metastasis

The roles of angiogenesis and the most prominent angiogenic vascular endothelial growth factor (VEGF) in diseases of the pancreas remain controversial. It was compared microvessel density (MVD) and VEGF status in normal pancreatic, chronic pancreatic, and pancreatic cancer (PC) tissues to establish their prognostic relevance. Eighty samples of PC tissue, 32 samples of normal pancreatic tissue, and 20 samples of chronic pancreatitis (cP) tissue were immunostained with monoclonal anti-CD31 and polyclonal anti-VEGF antibody. The MVD was correlated with clinicopathological features and survival. Microvessel density was higher in PC than in cP. Residual tumor status was highly predictive for survival. After stratification for residual tumor status, we identified lymph node metastasis (LNM) in more than two lymph nodes and high MVD as risk factors for mortality. Multivariate analysis

revealed only a high MVD (odds ratio 0.44) as an independent predictor of poor survival. Vascular endothelial growth factor was found over stromal cells in cP and over ductal adenocarcinoma cells in PC. Vascular endothelial growth factor expression status was not predictive of survival. The study confirms the role of angiogenesis in PC and identifies MVD as an independent prognostic factor in patients with curatively resected PC [398].

EGFR

Epidermal growth factor receptor (EGFR) has been considered as an attractive and potential therapeutic target of pancreatic cancer. However, the clinical importance of EGFR expression remains controversial. It was performed a meta-analysis of previous studies to quantitatively review the effects of EGFR expression on survival in patients with pancreatic cancer. Eight studies (570 patients) were included to perform a meta-analysis of the survival results. Overall, positivity for EGFR expression was 45 percent in pancreatic carcinoma. The combined hazard ratio was 1.23 (95 % confidence interval 1.01 to 1.48), indicating that EGFR expression has a significant impact on survival. Heterogeneity was absent between studies and publication bias, which suggests that the summary statistics obtained may approximate the actual average. Three trials reported a survival disadvantage for patients with EGFR expression will five trials reported no statistically significant difference. EGFR expression is a poor prognostic factor for survival in patients with pancreatic cancer [399].

D-dimer

Systemic activation of haemostasis is frequently observed in cancer patients, even in the absence of thrombosis. Moreover, this activation has been implicated in tumor progression, angiogenesis and metastatic spread. D-dimer, which is a degradation product of cross-linked fibrin, indicates a global activation of hemostasis and fibrinolysis. In a prospective and observational cohort study, it was assessed the prognostic value of D-dimer for overall survival and mortality risk in 1178 cancer patients included in the Vienna Cancer and Thrombosis Study. Patients were followed over 2 years at regular intervals until occurrence of symptomatic venous thromboembolism (VTE) or death. D-dimer levels were measured with a quantitative D-Dimer latex agglutination assay. Main tumor entities were malignancies of the lung (n=182), breast (n=157), lower gastrointestinal tract (n=133), pancreas (n=74), stomach (n=50), kidney (n=37), prostate (n=133), and brain (n=148); 201 had hematologic malignancies; 63 had other tumors. During a median follow-up of 731 days 460 (39.0%) patients died. The overall survival probabilities for patients with D-dimer levels categorized into four groups based on the 1st, 2nd and 3rd quartile of the D-dimer distribution in the total study population were 88, 82, 66 and 53 after 1 year, and 78, 66, 50 and 30 after 2 years, respectively. The univariate hazard ratio of D-dimer (per double increase) for mortality was 1.5 (95 % confidence interval 1.4 to 1.6) and remained increased in multivariable analysis including tumor subgroups, age, gender and VTE. It was concluded that high D-dimer levels were associated with poor overall survival and increased mortality risk in cancer patients [400].

CA 19-9

Radiation Therapy Oncology Group (RTOG) trial 9704 was the largest randomized trial to use adjuvant chemoradiation therapy for patients with pancreatic cancer. This report analyzes 5-year survival by serum level of tumor marker CA 19-9 of ≤90 vs >90 U/mL and compares results to those of the CONKO-001 trial. CA 19-9 expression was analyzed as a dichotomized variable (≤90 vs >90 U/mL). Cox proportional hazard models were used to identify the impact of the CA 19-9 value on overall survival (OS). Actuarial estimates of OS were calculated using the Kaplan-Meier method. Both univariate (hazard ratio 3.2) and multivariate (HR 3.1) analyses demonstrated a statistically significant decrease in OS for CA

19-9 serum level of ≥90 U/mL. For patients in the gemcitabine (Gem) treatment arm with CA 19-9 <90 U/mL, median survival was 21 months. For patients with CA 19-9 ≥90 U/mL, this number dropped to 10 months. In patients with pancreatic head tumors in the Gem treatment arm with RT quality assurance per protocol and CA 19-9 of <90 U/mL, median survival and 5-year rate were 24 months and 34 percent. In comparison, the median survival and 5-year OS rate for patients in the gemcitabine arm of the CONKO trial were 22 months and 21 percent. The analysis demonstrates that patients with postresection CA 19-9 values ≥90 U/mL had a significantly worse survival. Patients with pancreatic head tumors treated with gemcitabine with CA 19-9 serum level of <90 U/mL and per protocol RT had favorable survival compared to that seen in the CONKO trial [401].

Prognostic biomarkers

Patients with advanced stage adenocarcinoma of the pancreas have a poor prognosis. The identification of prognostic and/or predictive biomarkers may help stratify patients so that therapy can be individualized. Serum samples from patients enrolled in the Cancer and Leukemia Group B 80303 phase 3 trial, "Randomized Study of Gemcitabine With Versus Without Bevacizumab in Patients With Locally Advanced or Metastatic Adenocarcinoma of the Pancreas" were used to discover novel biomarkers. For the discovery phase, 40 sera were selected based on length of survival and type of therapy, and subjected to liquid chromatography coupled to tandem mass spectrometry analysis (LC-MS-MS). The top features (proteins) were then further selected for validation by enzyme-linked immunosorbent assay (ELISA). Quantification by nano-LC-MS-MS resulted in 1452 peptides mapping to 156 proteins across all 40 samples, 92 of which had 2 or more peptides. After curation of the data, the authors selected 1 putative prognostic protein, alpha 1-antichymotrypsin (AACT), and 2 putative predictive proteins, histidine-rich glycoprotein (HRG) and complement factor H (CFH), for validation by ELISA. AACT was found to be negatively correlated with overall survival. There was no evidence for interaction with bevacizumab and HRG, but there was some evidence for a weak positive correlation of HRG with overall survival. CFH was found to be neither a predictive nor a prognostic factor for overall survival. It was concluded that AACT may be a useful prognostic marker in patients with advanced stage pancreatic carcinoma, although additional validation studies are needed [402]

Diabetes after pancreatic resection

Glucose homeostasis is significantly altered immediately after partial pancreatectomy. The present study examined the long-term consequences of a hemipancreatectomy in 10 patients with chronic pancreatitis and 10 patients with benign pancreatic and extrapancreatic tumors. A 240-minute oral glucose challenge was performed before and shortly after pancreatic surgery, as well as after a follow-up of 3.1 ± 0.5 years. Plasma concentrations of glucose, insulin, and C-peptide were determined; and indices of insulin sensitivity and insulin secretion were calculated. In both groups of patients, fasting and postchallenge glucose concentrations were significantly altered immediately after surgery, but returned to preoperative levels at the time of follow-up. Postchallenge insulin and C-peptide concentrations were significantly reduced immediately after surgery, but were partly normalized at the time of follow-up. These changes were not accompanied by improvements in insulin sensitivity (Matsuda index). However, the oral disposition index revealed a significant recovery of beta-cell function at the time of follow-up. These findings demonstrate a capacity for recovery of glucose control after partial pancreatectomy and suggest that beta-cell function can improve significantly over time even in adult humans [403].

Pancreatic neoplasms during pregnancy

Neoplasms of the pancreas during pregnancy are rare, with less than 25 cases of benign and malignant tumors reported in the literature. Pancreatic neoplasms, both benign and malignant, are uncommon during pregnancy. There have been only eight reported cases of pancreatic adenocarcinoma, thirteen cases of cystic pancreatic lesions diagnosed during pregnancy, and three reported cases of pancreatic neuroendocrine tumors. Their occurrence during pregnancy leads to dilemmas in diagnosis, management, and timing of surgical treatment. In all cases the goal is to minimize both maternal and fetal risk. The timing of surgical resection for pancreatic neoplasms during pregnancy must take into account the risk of maternal disease progression and safety of the developing fetus. In addition, given the poor overall survival for patients with pancreatic adenocarcinoma, consideration and discussion of termination of the pregnancy are also important depending on the stage at diagnosis, gestational age at diagnosis, and maternal wishes/beliefs. It was presented three unique cases of pancreatic tumors occurring during pregnancy - one mucinous cystic neoplasm and two adenocarcinomas. Magnetic resonance imaging and ultrasound are the imaging modalities of choice in pregnancy. In patients with benign or premalignant tumors, surgical resection may be postponed until the second trimester. In symptomatic patients, or if there is a concern for intrauterine growth restriction, urgent surgical intervention should be performed. With malignant tumors, the benefit of delaying surgery must be balanced with the risk of maternal disease progression. Termination of the pregnancy should be discussed when a malignant tumor is diagnosed during the first trimester. Pancreatic tumors diagnosed during the third trimester may be resected after delivery. If malignant, early delivery of the fetus and subsequent maternal operation can be considered at appropriate fetal maturity. When these tumors occur during pregnancy, they present a diagnostic and treatment dilemma, with variation in treatment based on gestational age and patient preference. Adenocarcinomas of the pancreas during pregnancy present a unique treatment challenge. In the case of obvious malignancy (pancreatic adenocarcinoma, IPMN with invasive cancer, preoperatively diagnosed mucinous cystadenocarcinoma) there can be significant maternal consequences if definitive surgery or other therapy is delayed for fetal maturation. In a situation with inconclusive evidence of invasive malignancy, the surgeon and obstetrician must take into account the probability of malignancy in the pancreatic lesion, the gestational age of the fetus, and the wishes of the mother and family. With large pancreatic tumors (benign, pre-malignant, or malignant), most common in patients with MCNs, tumor size can cause complications during pregnancy; this includes intrauterine growth restriction (IUGR), compression of surrounding structures, pancreatitis, and tumor rupture. Endoscopic and transabdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are the primary imaging modalities used in diagnosing tumors of the pancreas. The risk to the fetus must be taken into account when imaging these tumors during pregnancy. Since its introduction into the field of medicine, diagnostic ultrasound has not been shown to be a health risk to either the fetus or the mother. Specifically, endoscopic ultrasound (EUS) may be used to gain information about tumor resectability and obtain a tissue diagnosis without an associated increase in radiation exposure. A single diagnostic CT scan is not associated with an increased risk of fetal malformations, although multiphase CT scans or repeat CT scans do increase the radiation exposure to the fetus, and should therefore be used sparingly. In addition, there may be an increased risk of spontaneous abortion associated with CT scanning within the first two weeks after conception (greater than the normal risk of spontaneous abortion during pregnancy of 15 %), and also a slightly increased risk of childhood cancers in an exposed fetus (one cancer per 500-1000 fetuses exposed to 0.03 Gy in utero). Several studies have failed to demonstrate an increase in fetal teratogenicity or acoustic nerve damage with the use of MRI or MRCP (magnetic resonance cholangiopancreatography). The lower fetal risk compared to CT and improved quality of imaging (when compared to transabdominal ultrasound) for making decisions regarding resectability make MRI the preferred imaging modality in pregnant patients. However, the use of gadolinium should be avoided in pregnancy, as the contrast is excreted by the fetus

and subsequently ingested into the gastrointestinal tract for an unknown period of time. Endoscopic retrograde cholangiopancreatography (ERCP) is also frequently used for diagnosis and biliary drainage for pancreatic masses causing obstructive jaundice. ERCP has been used during pregnancy. The estimated fetal radiation dose received during ERCP with fluoroscopy has been reported to be 0.0031 Gy, while the fetal radiation dose of a CT scan has been reported to be 0.024-0.03 Gy. Currently, the accepted teratogenic dose is 0.05-0.1 Gy. In all cases, patients who undergo ERCP during pregnancy should have a lead shield in place to minimize radiation exposure to the fetus. ERCP should be considered for biliary drainage if surgical intervention is not indicated or needs to be delayed in a jaundiced pregnant patient. ERCP is also indicated for acute cholangitis [404].

First trimester

Surgical intervention during the first trimester may be associated with spontaneous abortion or poor fetal outcome, including congenital anomalies. However, MCNs or IPMNs with obvious malignancy or high malignant potential (main duct variant IPMNs, larger tumors, the presence of mural nodules, multilocularity on imaging, and symptoms/signs such as jaundice, pain, and weight loss) diagnosed during the first trimester should be treated in a similar manner to malignant adenocarcinomas of the pancreas, with resection at the earliest safe opportunity. The benefit of delaying surgery for fetal maturity must be balanced with the risk of maternal disease progression. This decision must be carefully discussed with the patient [404].

Second trimester

The second trimester is the preferred time for surgical intervention for resectable pancreatic tumors. The American College of Obstetricians and Gynecologists' current recommendations are for operation during the second trimester for any nonurgent abdominal surgical procedures during pregnancy. Many authors of existing case reports agree that the second trimester is favorable for surgical resection, as fetal organogenesis is complete and the size of the fetus may allow for an easier surgical procedure in comparison to third trimester operations. In addition, the risk of spontaneous abortion is lowest during the second trimester. Three cases have been reported regarding adenocarcinoma of the pancreas diagnosed during the second trimester. One reported patient underwent successful surgical resection during the second trimester, while another underwent biliary diversion at 16 weeks. The third patient is the second reported case of a patient undergoing successful surgical resection of pancreatic adenocarcinoma during the second trimester. Pancreatic neuroendocrine tumors and cystadenomas have also been diagnosed during the second trimester of pregnancy. Typically, pancreatic neuroendocrine tumors behave more indolently and may be able to wait until after delivery in the asymptomatic patient. These should be resected during pregnancy if they are causing IUGR or other problems due to size [404]

Third trimester

Surgical resection of a pancreatic mass during the third trimester may be associated with an increased risk of premature induction of labor. However, since fetal maturity is typically achieved by this time, delivery may be performed early with postpartum surgical resection. Early delivery during the third trimester balances the benefit of survival of the fetus with the risk of maternal disease progression. Masses that are not clinically suspicious for malignancy may be expectantly managed until after full-term delivery. Immediate threat to the fetus or mother is an indication for early delivery and resection. Several cases have been reported of rupture of pancreatic tumors causing maternal instability during pregnancy. In this situation, emergent surgical intervention should take place, regardless of gestational age [404].

Unresectable tumors during pregnancy

Pancreatic tumors are frequently diagnosed at an advanced stage, and those occurring during pregnancy are no exception. Symptoms of a pancreatic mass, including abdominal discomfort and nausea, may be interpreted as normal symptoms of pregnancy, thus leading to a delayed diagnosis of adenocarcinoma and disease progression. Metastatic adenocarcinoma of the pancreas occurring during pregnancy has been reported five times in the literature. In these cases, the tumor was associated with complications such as pancreatitis, biliary obstruction, lung and liver metastases, hypercoagulability, and gastric outlet obstruction. Four of these patients died shortly after delivery [404].

Population-based results

USA

Surgical resection remains the only potentially curative option for patients with pancreatic adenocarcinoma (PAC). Advances in surgical technique and perioperative care have reduced perioperative mortality; however, temporal trends in perioperative morbidity and the use of adjuvant therapy on a population basis remain ill-defined. Using Surveillance, Epidemiology, and End Results-Medicare data, 2,461 patients with resected PAC were identified from 1991 to 2005. It was examined trends in preoperative comorbidity indices, adjuvant treatment, type of pancreatic resection, and changes in morbidity and mortality during 4 time intervals (ie, 1991-1996, 1997-2000, 2001-2003, and 2003-2005). The majority of patients underwent pancreaticoduodenectomy (n = 1,945; 79 %). There was a temporal increase in mean patient age and the number of patients with multiple preoperative comorbidities (Elixhauser comorbidities ≥3: 1991-1996, 10 % vs 2003-2005, 26 %). Perioperative morbidity (53 %) did not, however, change over time and 30-day mortality decreased by half (1991-1996: 6 % vs 2003-2005: 3 %). Overall, 51 percent (n=1,243) of patients received adjuvant therapy, with the majority receiving chemoradiation (n=817; 33 %). Among patients who received adjuvant therapy, factors associated with receipt of adjuvant chemotherapy alone relative to chemoradiation included older patient age (odds ratio 1.75) and ≥3 medical comorbidities (odds ratio 1.57). Receipt of adjuvant chemotherapy alone also increased over time (2003-2005 vs 1991-1996, odds ratio 2.21). Perioperative 30day mortality associated with resection for PAC decreased by one-half from 1991 to 2005. Although patients undergoing resection for PAC were older and had more preoperative comorbidities, the incidence of perioperative complications remained stable. The relative use of adjuvant chemotherapy alone vs chemoradiation therapy for PAC has increased in the United States during the 15 years examined [405].

Norway

It was reported results following pancreatic surgery at a tertiary referral hospital in Norway, and the experience with the effects of preoperative use of common bile duct stents, the prophylactic efficacy of octreotide, and explore significant survival factors in a prospective observational study of 275 patients during the years 1999-2009. Ninety-two ductal adenocarcinomas were operated, and 183 cases were inoperable. Pylorus preserving pancreatico-duodenectomy (PPPD) was performed in 42 cases, a classic Whipple procedure (WP) in 38, distal resection in 6 and total pancreatectomy in 6 patients. Median size of the tumours was 3 cm R(0) resection was obtained in 54 patients. Lymph node metastases were found in 64 patients. Twenty percent of patients experienced postoperative intra-abdominal complications, and 30 days postoperative mortality was 4 percent. A routine use of somatostatine analogues postoperatively did not reduce the frequency of leakage. Two years survival was 35 percent and 5 years 12 percent, respectively. It was concluded that patients

with ductal adenocarcinomas can be offered potential curative resections with acceptable rates of complication and mortality. Preoperative biliary stenting is still controversial and prophylactic octreotide should be used whenever the anastomosis is considered challenged and in cases of a soft pancreatic remnant. Five years all over survival has improved over the last decade from <5 percent to >11 percent [406].

Local recurrence

Loco (regional)-recurrence rate after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) remains high, and the efficiency of adjuvant chemoradiotherapy is still debated. It was aimed to assess predictors of loco-recurrence in order to tailor the indications for adjuvant chemoradiotherapy. Patients who underwent PD for PDAC between 2001 and 2010 were retrieved from a prospective database. Tumor recurrence was categorized as either loco-recurrence or distant recurrence. Clinicopathological characteristics and survivals were compared between patients with different recurrence patterns. The predictors for loco-recurrence were assessed. Seventy-nine patients were included. Loco-recurrence alone was identified in 22 patients (28 %), distant recurrence alone in 33 (42 %), both loco- and distant recurrences in 17 (22 %) and no recurrence in 7 (9 %). Median survival after recurrence (SAR) was significantly better in patients with locorecurrence alone than in those with distant recurrence alone (10 vs 5 months) or in those with both loco- and distant recurrences (10 vs 6 months); the survival for patients with distant recurrence alone and those with both patterns was identical. Patients with early recurrence had a significantly poorer SAR than those with late recurrence (median, 6 vs 9 months). Logistic regression analysis revealed that positive resection margin (HR 14.5; 95 % confidence interval 74 to 38), early T stage and large tumor size were the determinant factors directly related to loco-recurrence alone. It was concluded that patients with PDAC locorecurrence alone had a significantly better SAR than those with distant recurrence. Adjuvant chemoradiotherapy should be considered to reduce loco-recurrence further and improve long-term survival [407].

Loco (regional)-recurrence rate after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) remains high, and the efficiency of adjuvant chemoradiotherapy is still debated. It was aimed to assess predictors of loco-recurrence in order to tailor the indications for adjuvant chemoradiotherapy. Patients who underwent PD for PDAC between 2001 and 2010 were retrieved from a prospective database. Tumor recurrence was categorized as either loco-recurrence or distant recurrence. Clinicopathological characteristics and survivals were compared between patients with different recurrence patterns. The predictors for loco-recurrence were assessed. Seventy-nine patients were included. Loco-recurrence alone was identified in 22 patients (28 %), distant recurrence alone in 33 (42 %), both loco- and distant recurrences in 17 (22 %) and no recurrence in 7 (9 %). Median survival after recurrence (SAR) was significantly better in patients with locorecurrence alone than in those with distant recurrence alone (10 vs 5 months) or in those with both loco- and distant recurrences (10 vs 6 months); the survival for patients with distant recurrence alone and those with both patterns was identical. Patients with early recurrence had a significantly poorer SAR than those with late recurrence (median, 6 vs 9 months). Logistic regression analysis revealed that positive resection margin, T stage, and large tumor size were the determinant factors directly related to loco-recurrence alone. Thus, patients with PDAC loco-recurrence alone had a significantly better SAR than those with distant recurrence. Adjuvant chemoradiotherapy should be considered to reduce loco-recurrence further and improve long-term survival [408].

Venous thrombosis

It is now widely recognized that a strong correlation exists between cancer and aberrant hemostasis. Patients with various types of cancers, including pancreatic, colorectal, and gastric cancer, often develop thrombosis, a phenomenon commonly referred to as Trousseau syndrome. Reciprocally, components from the coagulation cascade also influence cancer progression. The primary initiator of coagulation, the transmembrane receptor tissue factor (TF), has gained considerable attention as a determinant of tumor progression. On complex formation with its ligand, coagulation factor VIIa, TF influences protease-activated receptor-dependent tumor cell behavior, and regulates integrin function, which facilitate tumor angiogenesis both in vitro and in mouse models. Furthermore, evidence exists that an alternatively spliced isoform of TF also affects tumor growth and tumor angiogenesis. In patient material, TF expression and TF cytoplasmic domain phosphorylation correlate with disease outcome in many, but not in all, cancer subtypes, suggesting that TF-dependent signal transduction events are a potential target for therapeutic intervention in selected types of cancer. In this review, we summarize our current understanding of the role of TF in tumor growth and metastasis, and speculate on anticancer therapy by targeting TF [409].

Portal hypertension

Sinistral, or left-sided, portal hypertension (SPH) is a rare cause of upper gastrointestinal hemorrhage. One retrospective analysis summarizes the clinical features of SPH and the results of surgical treatment. Between 2000 and 2009, patients from one hospital diagnosed with SPH were identified. Diagnosis of SPH was based on evidence of isolated splenic vein thrombosis, splenomegaly, gastroesophageal varices and exclusion of other causes of portal hypertension. mEight males and 5 females were included in the study, with a mean age of 44 ± 6 years (range: 31-68 years). Liver function was normal in all patients. Causes of SPH were chronic pancreatitis (n=7), pancreatic cancer (n=3), pancreatic cysts (n=2) and neuroendocrine tumor (n=1). The main clinical manifestations were gastrointestinal hemorrhage in 7 cases (54 %), upper abdominal pain in 10 (77 %) and hypersplenism in 12 (92 %). All patients had splenomegaly and gastroesophageal varices. Twelve patients underwent splenectomy and 1 received surgical removal of a pancreatic cyst. No major gastrointestinal tract rebleed occurred after a mean follow-up of 46 months (± 7 months). Two patients died of pancreatic cancer and 1 of acute myocardial infarction during follow-up. Thus, SPH should be suspected in patients with upper gastrointestinal varices as well as unexplained splenomegaly with normal liver function. Surgical intervention such as splenectomy offers a good long-term outcome in symptomatic patients [410].

Long-term survival

It was presented a case of carcinosarcoma of the pancreas in a 53-year-old woman. The carcinosarcoma was in the head of pancreas. She underwent a pancreaticoduodenectomy. The tumor was grossly yellowish-whitish. Histologic evaluation of the tumor revealed 2 elements separated from each other. One component was conventional pancreatic ductal adenocarcinoma, and the other component showed sarcomatous growth pattern composed of pleomorphic spindle cells. Immunohistochemically, the adenocarcinoma component was reactive for antibodies to cytokeratin 18 and epithelial membrane antigen. The sarcomatous component was reactive for smooth muscle antibody. These findings led to a diagnosis of pancreatic carcinosarcoma. The patient was treated with gemcitabine, adriamycin, and cisplatin after the operation. Although previously reported patients with pancreatic carcinosarcoma showed a very poor outcome, this patient has remained free of recurrence

for 20 months, which is the longest recurrence-free survival time recorded for this type of cancer [411].

Palliative resection

The objective of one study was to clarify the role of a palliative pancreaticoduodenectomy in both pancreatic and periampullary adenocarcinomas. Survival outcomes were compared between resections and bypass operations, and between curative (R0) and palliative resections, with a microscopically (R1) and a grossly (R2) positive resection margin. There were 595 surgical patients, including 207 undergoing bypass operations and 388 undergoing pancreaticoduodenectomies, with 47 percent curative resections (R0) and 18 percent palliative resections (R1 + R2). The overall positive margin rate after a pancreaticoduodenectomy was 27 percent (R1 = 8 %, R2 = 19 %). For periampullary adenocarcinomas, there was a significant survival difference between the R0, palliative, and no resection groups. However, there was no significant survival difference between the R0 and palliative resection for pancreatic head adenocarcinoma. Note that the survival outcome after either a curative or a palliative pancreaticoduodenectomy was still better than the survival outcome of a bypass operation. There was a survival benefit after a pancreaticoduodenectomy regardless of the resection margin or primary origin of the periampullary adenocarcinoma, as compared with a bypass operation. The resection margin after a pancreaticoduodenectomy did not play a role in the survival outcome in pancreatic head adenocarcinoma. Therefore, it was recommended that pancreaticoduodenectomies should be attempted whenever possible [412].

Other palliation

Surgical interventions

Pancreatic cancer is an aggressive malignant disease with increasing incidence. Radical resection, the only potentially curative method, is possible in only 20-30 percent of patients. The main symptoms of advanced non-resectable pancreatic head tumors include obstructive jaundice, caused by stenosis of distal common bile duct, duodenal obstruction and pain, especially in the epigastric region and back. The aim of palliative treatment is to relieve these complaints. One paper evaluated the palliative surgical treatment results in patients with pancreatic head and periampullary region cancer. The study included all patients with pancreatic head and periampullary region cancer who underwent surgery in a university hospital 2006 to 2010. The aim of the surgery in all patients was to resect the tumor. Palliative surgical procedure was performed in patients with an inoperable tumor. It was performed gastro-entero anastomosis in all the patients. When perioperative situation allowed, hepatico-jejuno anastomosis was performed in patients with obstructive jaundice. Surgical splanchnicectomy was performed in patients with back pain. Over five years, it was performed a surgery in 94 patients for malignant disease of pancreas and periampullary region. Radical resection was performed in 45 patients. Palliative bypass procedure was performed in 42 patients. Exploration only was performed in 7 patients. Postoperative complications after palliative bypass procedures were noted in 15 patients (31 %), the majority of these complications were minor. It was concluded that the advantage of surgical hepaticojejunal anastomosis over endoscopically placed stent, particularly in superior longterm patency. Therefore, it is advisable to perform these procedures in patients with longer expected survival. Morbidity associated with palliative surgical procedures was relatively low and there was no mortality [413].

Endoscopic stenting versus operative gastrojejunostomy

Malignant gastric outlet obstruction represents a terminal stage in pancreatic cancer. Between 5 and 25 percent of patients with pancreatic cancer ultimately experience malignant gastric outlet obstruction. The aim in palliating patients with malignant gastric outlet obstruction is to reestablish an oral intake by restoring gastrointestinal continuity. This ultimately improves their quality of life in the advanced stages of cancer. The main drawback to operative bypass is the high incidence of delayed gastric emptying, particularly in this group of patients with symptomatic obstruction. One study aimed to compare surgical gastrojejunostomy and endoscopic stenting in palliation of malignant gastric outlet obstruction, acknowledging the diversity and heterogeneity of patients with this presentation. A retrospective study investigated patients treated for malignant gastric outlet obstruction from 1998 to 2008. Endoscopic duodenal stenting was performed under fluoroscopic guidance for placement of the stent. The operative patients underwent open surgical gastrojejunostomy. The outcomes assessed included time to diet, hospital length of stay (LOS), biliary drainage procedures, morbidity, and mortality. Of the 45 participants in this study, 26 underwent duodenal stenting and 19 had operative bypass. Comparing the stenting and operative patients, the median time to fluid intake was respectively 0 versus 7 days, and the time to intake of solids was 2 versus 9 days. The median total LOS was shorter in the stenting group (11 vs 25 days), as was the median postprocedure LOS (5 vs 10 days). Endoscopic stenting is thus preferable to operative gastrojejunostomy in terms of shorter LOS, faster return to fluids and solids, and reduced morbidity and in-hospital mortality for patients with a limited life span [414].

Quality of life

Depression

It was recently reviewed the association of pancreatic cancer with depression. Pancreatic cancer is commonly perceived by the public of being a painful and deadly disease, which leads to fear in patients diagnosed with pancreatic cancer that might lead to anxiety and depression. Depression in pancreatic cancer has been reported to have a higher prevalence than in patients with other types of gastrointestinal carcinomas. The range of reported depression varies widely, from 10 to 75 percent, depending on the instruments used for evaluation and when the evaluation was performed relative to diagnosis and treatment. While the link has been known for ages, the relationship is still poorly understood and understudied. Recent studies evaluating patient-reported outcomes list depressive symptoms at 40 percent for pancreatic cancer. Depression and anxiety may even precede the diagnosis of pancreatic cancer. Anxiety, including presentation with panic attacks, has been reported prior to the diagnosis of pancreatic cancer. An investigation of signs and symptoms of pancreatic cancer by a population-based case-control study found that patients with pancreatic cancer were more likely to report altered ability to sleep than controls (OR 2.9). Although pain has been examined as a correlate of depression, it appears that there may be a physiologic cause for pain as well. However, the details and spectrum of psychosocial distress and depression in pancreatic cancer patients have not been fully investigated. A recent review confirmed the linkage between pancreatic cancer and depression but was unable to explain the cause or a direct coping style affecting survival. An analysis of 50 inpatient pancreatic cancer inpatients in China revealed that the link between depression and pancreatic cancer is common. A recent population analysis in the Netherlands of 120,852 individuals found a modest decrease in risk of pancreatic cancer associated with past sports activity. However, a prior systematic review did not find a strong evidence of a link with physical activity and pancreatic cancer. A particular association of depression with pancreatic carcinoma has been previously proposed, with Yaskin reporting depression, anxiety, and

insomnia as the presenting symptoms for pancreatic cancer as early as 1931. When compared with patients with gastric adenocarcinoma, pancreatic cancer patients were more likely to fulfill criteria for major depressive disorder within one year prior to diagnosis or at the time of diagnosis. A population-based case-control study found that there was an increase in altered ability to sleep (OR 2.9) reported in cases compared to controls within 3 years before diagnosis with pancreatic cancer. Additionally, a relationship between depression and pancreatic cancer was found in the general population using a longitudinal population-based study with depression more commonly preceding pancreatic cancer than other malignancies (OR 4.1). Taken together, these data suggest that the relationship between depression, anxiety, insomnia, or sleep related disturbances and pancreatic cancer is likely to be due to more than poor prognosis or fear of pain. Another area of recent interest is the relationship between sleep and cancer. A symptom-based approach focuses on the insomnia and daytime sleepiness. A case report of abnormal sleep behavior, similar to sleep-related epilepsy, parasomnia, and night delirium, became a subsequent diagnosis of a tumor in the pancreas which demonstrates how sleep disturbances can precede the diagnosis. Moreover, self-reported sleep disturbances increase during chemotherapy in pancreatic cancer patients. However, the relationship among depression, sleep, and anxiety treatment side effects and response is complex and has not been adequately studied in pancreatic cancer. Results of screening for depression, sleep-related disturbances, and anxiety in patients with diagnosed adenocarcinoma of the pancreas were now evaluated at initial consultation and subsequent visits at the multidisciplinary pancreatic cancer clinic at our University Cancer Center. Cross-sectional and longitudinal psychosocial distress was assessed utilizing Personal Health Questionnaire 9 (PHQ9) to screen for depression and monitor symptoms, the Penn State Worry Questionnaire (PSWQ) for generalized anxiety, and the University of Michigan Sleep Questionnaire to monitor sleep symptoms. Twenty-two patients diagnosed with pancreatic cancer participated during the 6-month pilot study with longitudinal followup for thirteen patients. In this study, mild-to-moderate depressive symptoms, anxiety, and potential sleep problems were common. The main finding of the study was that 23 percent of the patients who were part of this pilot project screened positive for moderately severe major depressive symptoms, likely anxiety disorder or a potential sleep disorder during the study. One patient screened positive for moderately severe depressive symptoms in longitudinal followup. It was concluded that depression, anxiety, and sleep problems are evident in patients with pancreatic cancer. Prospective, longitudinal studies, with larger groups of patients, are needed to determine if these comorbid symptoms impact outcome and clinical course. Another finding from this study which is not represented in the statistical outcome is the routine collection of psychometric data in a busy multidisciplinary pancreatic cancer clinic. A large percentage (90 %) of patients was not willing to use the tablet PC; the routine collection of psychometric data was accomplished through the traditional methods of pen and paper. Concerns about the validity of the measurement being conducted on the tablets are not founded in this study; however future research is warranted. Future trials should consider the challenges of using tablet PCs and have alternative methods for a successful project. Most cancer centers have patient education material on psychooncology, and referrals are common: however the use of psychometric surveys is a more proactive approach for screening for acute mental health disorders. Obviously the complex nature of the interaction between the cancer, knowledge of the diagnosis, side effects of chemo and radiation therapy, and previous history of mental will not be revealed in a simple psychometric survey; the data can help inform and engage patients and clinicians to address concerns and seek out additional services. While current oncology guidelines focus on distress management, the nature of anxiety, depression, and sleep disorders may not be revealed by focusing on distress. Future studies should evaluate the differences between the distress thermometer and other psychometric tests. Sleep disturbance accounted for 16 percent of the variance in depressive symptoms. Sleep was also more disturbed in those with a more advanced stage of cancer. If, as we believe, that poor sleep contributes to both poor quality of life and increased depression in cancer patients, then there is good reason to pursue improving sleep in these patients. Future studies should be significantly powered to better describe the

relationship among these variables and to explore strategies for improving sleep. Behavioral interventions have been shown to be effective in improving sleep in other cancers and are particularly appealing in patients already undergoing rigorous treatment. Compared to previous studies, the individual prevalence of anxiety, depression, and sleep disorders appears to be lower than previously reported. While the number of participants is large in comparison to historical reports of pancreatic cancer and depression, the numbers are insufficient for a robust statistical analysis. In a larger retrospective series of 258 patients with pancreatic cancer, depression did not affect survival, although it was common with 54 out of 258 patients (21 %) with a diagnosis and treatment for depression at the time of the pancreatic cancer diagnosis. The median survival time for depressed patients was 4 months compared with non-depressed patient's median survival time of 5 months (not significant). There was also no association of cancer stage to the presence of depression. These findings are in agreement with our findings of a lack of major depressive symptoms, anxiety, and sleep disorders in patients presenting to a dedicated pancreatic cancer clinic. However, retrospective diagnosis of depression can lead to lower prevalence diagnosis. The prospective trial does shed some light on how sleep, anxiety, and depression symptoms are present using objective psychometric instruments. The lack of statistical correlation with survival does not reduce the need to evaluate and treat the symptoms in patients. It is possible that the decrease in reported psychosocial distress in ours and in Kelsen's studies reflects changes in attitudes among pancreatic cancer patients. Another explanation is that prior reports did not utilize a prospective, standardized screening which was utilized here. An alternate explanation may be that in both of our studies patients presented to a comprehensive cancer center and were therefore motivated to seek care, which may suggest bias in our patient population. Additional study is warranted to further evaluate the prevalence and the correlation to improve the lives of patients diagnosed with pancreatic cancer. Future plans to design a larger prospective study examining the correlation between the three comorbidities and pancreatic cancer with comparison against a control group are needed. Additional data collection about the treatment modalities and prior mental health history will add additional insight into this complex relationship [415].

Neoadjuvants before radically intended surgery

For over 25 years, the standard of care for resectable pancreatic adenocarcinoma has been upfront surgery followed by delivery of post-operative therapy. Until recently however, there has been no consensus as what constituted a standard adjuvant regimen. Data from large phase III studies now support single agent gemcitabine, administered over 6 cycles, as standard. Nevertheless, the overall survival of patients undergoing upfront surgical resection followed by adjuvant therapy remains poor, with no significant improvements in median, or long term survival over the last 3 decades. Surgery as the first intervention for potentially curative pancreatic cancer has some distinct disadvantages and neoadjuvant therapy provides a mechanism to better select patients for subsequent surgical intervention. Current data suggest this approach spares patients from a morbid surgical procedure when it will be of no benefit and improves outcomes for those who do undergo surgery. Furthermore, with the increasing recognition of borderline resectable pancreatic cancer, neoadjuvant treatment should be considered as alternative to upfront surgery for this distinct clinical entity. This has the potential to maximize the chances of a margin-negative resection and minimize the number of patients harboring aggressive disease from undergoing a fruitless surgical procedure. Importantly, as the number of targeted agents available for clinical use expands, more rational, personalized neoadjuvant therapies may emerge [416].

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The objective of this study was to compare survival between all patients with radiographically resectable adenocarcinoma of the proximal pancreas who underwent preoperative chemoradiation therapy (PRE-OP CRT) or surgical exploration first (SURGERY) with "intention to resect." Pancreatic cancer patients who undergo resection after PREOP CRT live longer than patients who undergo resection without PREOP CRT, a difference that may be attributable to patient selection. It was retrospectively identified 236 patients with pancreatic head adenocarcinoma seen between 1999 and 2007 with sufficient data to be confirmed medically and radiographically resectable. The outcomes of 144 patients who underwent PREOP CRT were compared to those of 92 patients who proceeded straight to SURGERY. The groups were similar in age and gender. Tumors were slightly larger in the PREOP CRT group (mean 2.5 cm vs 2.1 cm), and there were trends toward more venous abutment (54 % vs 39 %) and a higher Charlson comorbidity index. In the PREOP CRT group, 76 patients (53 %) underwent resection, 28 (19 %) had metastatic and 17 (12 %) locally unresectable disease after PREOP CRT, and 23 (16 %) were not explored due to performance status or loss to follow-up. In the SURGERY group, 68 patients (74 %) underwent resection. Sixteen patients (17 %) had metastatic and eight patients (9 %) locally unresectable disease at exploration. In patients who underwent resection, the PREOP CRT group had smaller pathologic tumor size and lower incidence of positive lymph nodes than the SURGERY group but no difference in positive margins or need for vascular resection. Median overall survival (OS) in patients undergoing resection was 27 months in the PREOP CRT group and 17 months in the SURGERY group. Median OS in all patients treated with PREOP CRT or surgically explored with intention to resect was 15 and 13 months, respectively, with superimposable survival curves. Despite a lower resection rate, the PREOP CRT group as a whole had a similar OS to the SURGERY group as a whole. For patients who underwent resection, those in the PREOP CRT had longer survival than those in the SURGERY group, suggesting that PREOP CRT allows better patient selection for resection. PREOP CRT should be considered an acceptable alternative for most patients with resectable pancreatic cancer [419].

In borderline patients

Margin-negative pancreatectomy provides only chance to cure pancreatic cancer. However, borderline resectable pancreatic cancer (BRPCa) has the risk of incomplete palliative resection. It was retrospectively reviewed 32 patients with BRPCa who underwent a pancreatectomy following preoperative chemoradiation therapy (CCRT (+)/Px group) and compared these patients with those with resectable pancreatic cancer (RPCa) who underwent pancreatectomy without preoperative CCRT (CCRT (-)/Px group, n=104). Eighteen patients (56 %) showed more than 50 percent significant pathological response to CCRT. The degree of pathological responses showed a positive relationship between final pT stage. More frequent vascular resection, transfusion, and longer operation time were observed in the CCRT(+)/Px group. However, similar R0 resection rates, lower pT stage,
smaller number of metastastic lymph nodes, and lower incidence of lymph node metastasis were noted in the CCRT(+)/Px group. The overall disease-specific survival were similar (median survival, 31 months vs 26 months) and no statistical differences in cancer recurrence risks were noted between the two groups. It was concluded that pancreatectomy following preoperative neoadjuvant CCRT can be a potential strategy for margin-negative resection in BRPCa patients [420].

Neoadjuvant treatment frequently is performed in unresectable/borderline resectable pancreatic cancer. The aim of thoneis study was to retrospectively compare postoperative outcomes and survival of patients who underwent pancreatectomy after neoadjuvant treatment for locally advanced/borderline resectable pancreatic cancer (neoadjuvant treatment group) with those of patients with resectable disease who underwent upfront surgery. Between 2000 and 2008, there were 403 patients who underwent pancreatic cancer resection, 41 (10 %) patients after neoadjuvant treatment for initially unresectable tumors and 362 (90 %) patients had upfront surgery. Univariate and multivariable analyses were performed. Mortality/morbidity rates were similar in the 2 groups. Nodal metastases were significantly lower in the neoadjuvant treatment group (32 % vs 86 %). A complete pathologic response was observed in 14 percent after neoadjuvant treatment. Median disease-specific survival from resection was 35 and 27 months in the neoadjuvant treatment and upfront groups, respectively. In the neoadjuvant treatment group survival rates were similar in N0/N1 patients. It was concluded that postoperative mortality and morbidity do not significantly increase after neoadjuvant treatment. Neoadjuvant treatment in locally advanced pancreatic cancer can lead to an objective pathologic response, but this does not significantly improve survival after resection [421].

Chemoradiotherapy

Although the prognostic benefit of neoadjuvant chemoradiotherapy (NCRT) against pancreatic cancer has been indicated by several reports, it is controversial whether histological response is associated with prognosis. The objective was to explore the relationship between histological response and prognosis in T3 and T4 pancreatic adenocarcinoma. It was histologically examined the resected specimens obtained from 58 patients (T3, n=40; and T4, n=18) for whom we performed curative-intent resection after NCRT. Histological response was evaluated according to Evans's criteria to determine whether it influenced survival. In T3 tumors, 13 (33 %) belonged to high responders (tumor destruction of >50 %) (R0, n=13) and 27 (68 %) belonged to low responders (tumor destruction of ≤50 %) (R0, n=22, R1, n=3, R2, n=2). Recurrence-free survival rate was significantly higher in high responders than in low responders (3-year recurrence-free survival rates: 71 % vs 13 %). In T4 tumors, however, only 1 (6 %) was a high responder, and R0 resection was obtained only in 5 patients (28 %). In T3 tumors, histological response is considered a significant prognostic indicator, securing the surgical margin, whereas in T4 tumors, NCRT did not provide beneficial histological response, not securing the surgical margin [422].

Complete response

In patients with pancreatic ductal adenocarcinoma (PDA) who received neoadjuvant therapy and pancreatectomy, pathologic complete response (pCR) is rarely observed and the prognostic significance of pCR is not clear. In one study, it was identified 11 patients with pCR (3 %) from 442 patients with PDA who received neoadjuvant treatment and pancreatectomy from 1995 to 2010. There were 6 men and 5 women, with a median age of 61 years. Four patients had either synchronous or history of extrapancreatic cancer. Five patients received neoadjuvant chemotherapy followed by chemoradiation, and 6 received chemoradiation alone. Ten patients had pancreaticoduodenectomy, and 1 had distal pancreatectomy. Scar and chronic pancreatitis consistent with therapy effect were present in all cases (100 %). Pancreatic intraepithelial neoplasia (PanIN) 3/carcinoma in situ was present in 5 cases, and PanIN1 and PanIN2 in 5 cases. However, no residual invasive carcinoma or lymph node metastasis was identified in all cases. Follow-up information was available in 10 patients. Follow-up time ranges from 6 to 194 months (median, 63 months). During the follow-up, 3 patients died of other causes, and 1 developed a second primary PDA in the tail of the pancreas at 84 months after the initial pancreaticoduodenectomy and died at 105 months after the initial diagnosis of PDA. The other 6 patients were alive with no evidence of disease. Patients with pCR had a better survival than did those who had posttherapy stage I or IIA disease. Patients with PDA who received neoadjuvant therapy and had pCR in pancreatectomy are rare but have a better prognosis [423].

Predictive factors for recurrence

To analyze the histopathological indicators significantly associated with surgical outcome and the pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy (CRT) and subsequent pancreatectomy a study was performed. Clinicopathological assessment of the resected specimen is an indispensable tool for predicting patient prognosis and localizing high-risk sites for tumor relapse. This procedure is also essential for the establishment of efficient postoperative follow-up protocols in the setting of a preoperative CRT strategy. In a prospective phase II clinical trial, 110 patients received preoperative CRT and subsequent resection. All 110 resected cases were included in this study. It was employed disease-free survival (DFS) as a surgical outcome, and the pattern of recurrence was divided into 2 categories: recurrence in the abdominal cavity (RAC), defined as either a locoregional or a peritoneal recurrence; or distant recurrence (DR), defined as cancer recurrence in a distant organ. Clinicopathological variables were analyzed in association with DFS, RAC, and DR. Positive nodal involvement and perineural invasion were independent factors that were significantly associated with an unfavorable DFS. The presence of perineural invasion was the single independent variable significantly associated with an increased risk of RAC, whereas the status of nodal involvement was the single independent variable significantly associated with an increased risk of DR. It was concluded that the status of nodal involvement and perineural invasion in resected specimens are significantly associated with DFS and clearly predict the pattern of recurrence in the setting of a preoperative gemcitabine-based CRT strategy [424].

Adjuvants to radical surgery

In Radiation Therapy Oncology Group 9704, as previously published, patients with resected pancreatic adenocarcinoma received continuous infusion 5-FU and concurrent radiotherapy (5FU-RT). 5FU-RT treatment was preceded and followed by randomly assigned chemotherapy, either 5-FU or gemcitabine. One analysis explored whether failure to adhere to specified RT guidelines influenced survival and/or toxicity. RT requirements were protocol specified. Adherence was scored as per protocol (PP) or less than per protocol (<PP). Scoring occurred after therapy but before trial analysis and without knowledge of individual patient treatment outcomes. Scoring was done for all tumor locations and for the subset of pancreatic head location. RT was scored for 416 patients: 216 PP and 200 <PP. For all pancreatic sites (head, body/tail) median survival (MS) for PP versus <PP was 1.74 versus 1.46 years. In multivariate analysis, PP versus <PP score correlated more strongly with MS than assigned treatment arm; for patients with pancreatic head tumors, both PP score and gemcitabine treatment correlated with improved MS. For all tumor locations, PP score was associated with decreased risk of failure and, for gemcitabine patients, a trend toward reduced Grade 4/5 nonhematologic toxicity. This is the first phase III, multicenter, adjuvant protocol for pancreatic adenocarcinoma to evaluate the impact of adherence to specified RT

protocol guidelines on protocol outcomes. Failure to adhere to specified RT guidelines was associated with reduced survival and, for patients receiving gemcitabine, trend toward increased nonhematologic toxicity [425].

Carbon-ion radiotherapy (CIRT)

The authors evaluated the tolerance and efficacy of carbon-ion radiotherapy (CIRT) as a short-course, preoperative treatment and determined the recommended dose needed to reduce the risk of postoperative local recurrence without excess injury to normal tissue. Patients radiographically defined with potentially resectable pancreatic cancer were eligible. A preoperative, short-course, dose-escalation study was performed with fixed 8 fractions in 2 weeks. The dose of irradiation was increased by 5 percent increments from 30 grays equivalents (GyE) to 36.8 GyE. Surgery was to be performed 2 to 4 weeks after the completion of CIRT. The study enrolled 26 patients. At the time of restaging after CIRT, disease progression with distant metastasis or refusal ruled out 5 patients from surgery. Twenty-one of 26 patients (81 %) patients underwent surgery. The pattern of initial disease progression was distant metastasis in 17 patients (65 %) and regional recurrence in 2 patients (8 %). No patients experienced local recurrence. The 5-year survival rates for all 26 patients and for those who underwent surgery were 42 percent and 52 percent, respectively. Thus, preoperative, short-course CIRT followed by surgery is feasible and tolerable without unacceptable morbidity [426].

Adjuvants to radical surgery

Hyperthermic intraperitoneal intraoperative chemotherapy

Five-year survival in patients with pancreatic cancer is poor. Surgical resection is the only potentially curative resection. The results of adjuvant treatment either with chemotherapy or with radiotherapy have been contradictory and the incidence of local-regional recurrence remains high. If local-regional recurrence is controlled survival may be expected to increase. The sites of recurrence after curative resection are the liver in 50-60 percent, the peritoneal surfaces in 40-50 percent, and the pancreatic bed in 50 percent of the cases. The pathophysiology of local-regional recurrence after R0 resection remains an enigma. It may be the result of metastases undetected on imaging or laparotomy or tumor dissemination and implantation of cancer emboli at the resection sites may occur with pancreatectomy. If this is true then intraperitoneal chemotherapy may be the treatment that has a beneficial impact on overall survival by reducing the number of local-regional recurrences. Intraperitoneal chemotherapy has the capability to eradicate the microscopic cancer emboli and reduce the incidence of local-regional recurrences. It is obvious that there is an absolute need for adjuvant treatment in addition to surgical resection. Although the pathophysiology of localregional recurrence is unclear it has been assumed that the resection of a tumor located within narrow margins of resection may result in tumor dissemination because of interstitial tissue trauma, or severed lymphatics leaking cancer cells, or from venous blood loss contaminated by cancer cells. The disseminated cancer emboli are trapped in fibrin, stimulated by growth factors, and give rise to local-regional recurrent tumors within monthsyears after initial surgical manipulations. The eradication of the entrapped microscopic cancer emboli may be possible by using intraperitoneal chemotherapy. Intraperitoneal chemotherapy has been shown to be very effective in carcinomatosis from colorectal cancer either as HIPEC or as early postoperative intraperitoneal chemotherapy (EPIC) under normothermia. The advantage of intraperitoneal chemotherapy is the high drug level that can be achieved by low systemic exposure. Gemcitabine as systemic adjuvant treatment has not been confirmed to assist in control of local disease. In contrast, it has been shown both from laboratory and clinical studies that the intraperitoneal use of gemcitabine may effectively

target local disease. Laboratory studies have shown that the intraoperative use of gemcitabine may effectively prevent the development of peritoneal metastases. In addition early postoperative intraperitoneal chemotherapy may reduce the extent of peritoneal metastases. Data shows that the intraperitoneal use of gemcitabine in patients having pancreatectomy is well tolerated and does not produce severe toxicity. Intraperitoneal gemcitabine may be incriminated for anastomotic failures although it has not been proved. The large concentration of gemcitabine sustained in the peritoneal space and the low plasma concentration are findings supporting its intraperitoneal use. Pharmacokinetic studies of intraperitoneal administration in a rat model have demonstrated that the area under the curve ratio of intraperitoneal to systemic drug exposure is closely related to the intraperitoneal dose and tissue samples showed increased drug concentration when administered with heat. Preliminary pharmacokinetic data in patients with resectable pancreatic cancer that underwent HIPEC with gemcitabine at a dose of 1000 mg/m² showed marked local-regional drug exposure. In addition, the intraperitoneal use of gemcitabine in clinical practice has shown equal results to platinum-based regimens in women with ovarian cancer. These data taken together suggest that studies to test gemcitabine in patients with resectable pancreatic cancer are justified. It appears that intraperitoneal chemotherapy may have a favorable effect in eradicating microscopic cancer emboli not only locoregionally but also in the portal venous circulation. It has been found that the measured portal vein concentrations exceeded the measured concentration in other vessels when 5-FU was administered intraperitoneally. Although the number of the included patients is very small and the median follow-up time short, no patient developed local-regional recurrence. This implies that HIPEC is likely to be effective in eradicating residual microscopic cancer emboli at the peritoneal surfaces. Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) may be used in order to control local-regional recurrences. The purpose of one study was to identify the effect of HIPEC in patients with pancreatic cancer undergoing potentially resection. From 2007-2011, 21 patients, mean age 69 \pm 10 (50-86) years, underwent tumor resection, and HIPEC with gemcitabine. The hospital mortality and morbidity rate was 10 percent and 33 percent, respectively. Five-year and median survival was 23 percent and 11 months, respectively. The recurrence rate was 50 percent but no patient developed local-regional recurrence. No patient was recorded with gemcitabine-induced toxicity. This clinical study of 21 patients is the first to combine an R0 pancreas cancer resection with HIPEC. Increased morbidity and mortality from intraoperative gemcitabine was not apparent. Patients with pancreatic cancer undergoing potentially curative resection in combination with HIPEC may be offered a survival benefit. Data suggested that local-regional recurrences may be greatly reduced. Further studies with greater number of patients are required to confirm these findings [427].

Pharmacological therapy generalized disease

Overview

Pancreatic cancer belongs to the most malignant gastrointestinal cancers and, in its advanced stage, remains a deadly disease for nearly all affected patients. Treatment of metastatic adenocarcinoma of the pancreas not only involves chemotherapy and targeted therapy, but also requires attention to accompanying comorbidities as well as frequently intensive supportive treatment and psychosocial support. Gemcitabine-based combinations with fluoropyrimidines and platin analogs have essentially failed to provide a substantial prolongation of survival and may constitute a treatment option only in patients with a good performance status. Among targeted therapies, only the EGFR tyrosine kinase inhibitor erlotinib has shown activity which is marginal in the overall population, but clinically relevant in patients developing skin rash. New avenues of polychemotherapy are presently explored since the gemcitabine-free FOLFIRINOX-regimen (infusional 5-fluorouracil/folinic acid plus irinotecan and oxaliplatin) was shown to be markedly superior to gemcitabine in selected good-performance patients. Pancreatic cancer is notably characterized as a hypovascular

tumor rich in desmoplastic stromal tissue. An innovative approach to treatment therefore focuses on peritumoral fibroblasts and aims to induce a depletion of the stroma either by inhibition of the hedgehog pathway or by targeting SPARC (secreted protein acidic and rich in cysteine) via application of albumin-bound paclitaxel [428].

Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths in the US and Europe, and the lethality of this cancer is demonstrated by the fact that the annual incidences are approximately equal to the annual deaths. Current therapy for PC is multimodal, involving surgery and chemotherapy. Clinical symptoms are unspecific, and consequently about 85% of patients with PC are diagnosed at advanced tumor stages without any surgical therapy options. Since the therapeutic rates for PC are so dismal, it is essential to review the clinical targets for diagnosis and treatment of this lethal cancer. In one review, it was discussed potential treatment options for PC by identifying molecular targets including those involved in cell proliferation, survival, migration, invasion and angiogenesis. Targeting these molecules in combination with surgery could improve the clinical outcome for PC patients. For a decade, gemcitabine has remained the single first-line chemotherapeutic agent for advanced adenocarcinoma of the pancreas; however, less than 25 percent of patients benefit from gemcitabine. The reason for frequent reoccurrence of PC after conventional methods such as surgery, radiation and/or chemotherapy is due to the lack of understanding of the basic underlying metabolic cause of the cancer and thus consequently remains uncorrected. The understanding of drug resistance in PC is still not clear and may be answered by focusing on new useful biomarkers and their role in chemo- and radioresistance [429].

Gemcitabine

Gemcitabine potential myotoxicity has been described in several cases of radiation recall and in patients treated with gemcitabine alone or in combination with other chemotherapy agents. It was reported two cases of gemcitabine related myositis identified at one institution, and perform a literature review of cases which meet the criteria for gemcitabine induced myositis associated to either radiation therapy or chemotherapy alone [430].

Gemcitabine and oxaliplatin

One study evaluated activity and toxicity of modulated doses of gemcitabine associated to oxaliplatin in patients with secondary CIRS and with locally advanced pancreatic adenocarcinoma (LAPC) and metastatic pancreatic adenocarcinoma (MPC). Since January 2006, untreated LAPC and MPC patients have been assessed with ADL, IADL, CIRS to modulate chemotherapy dosages according to co-morbidity stage. Patiens aged<75 years, co-morbidity stage primary/intermediate, or ≥75 years and co-morbidity stage primary, received gemcitabine 1,000 mg/m² as a 10 mg/m²/min infusion on day 1 and oxaliplatin 70 mg/m² as a 2-h infusion on day 2 every 2 weeks. Patiens aged<75 years, co-morbidity stage secondary or ≥75 years and co-morbidity stage intermediate/secondary patients received gemcitabine 800 mg/m². Primary endpoint was the overall response rate (ORR). Secondary endpoints were disease control rate (DCR), PFS, OS and toxicity. Thirty-one patients were recruited: 26 percent (8/31) LAPC and 74 percent (23/31) MPC; median age 69 years. Comorbidity stage primary/intermediate, 19; secondary, 12. Twenty-seven valuable patients: ORR 30 percent disease control rate 85 percent. Median follow-up 13 months: median PFS and OS were 6 and 15 months, respectively. Valuable cycles 140. Grade 3/4 toxicity per patient: leukopenia, 19 percent; neutropenia, 56 percent; thrombocytopenia, 7 percent; SGOT/SGPT, 7 percent; gamma-GT, 7 percent; fever without neutropenia, 4 percent. Median received dose intensity: gemcitabine 400 mg/m²/w; oxaliplatin 35 mg/m2/w. Modulation of GemOx chemotherapy according, to CIRS stage in advanced pancreatic cancer confirms reported efficacy and tolerability [431].

Gemcitabine, docetaxel and capecitabine (GTX)

It was evaluated the activity and tolerance of gemcitabine in combination with docetaxel and capecitabine in previously untreated patients with advanced pancreatic cancer. Chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer were treated with gemcitabine (1,500 mg/m² on days 1 and 15), docetaxel (50 mg/m² on days 1 and 15) and capecitabine (2,250 mg/m², orally in two daily divided doses, on days 1-7 and 15-21). All three drugs were administered in 4-week cycles, in an initial prospective plan of six cycles. The primary end-point was response rate. Forty patients were enrolled in the study. At the time of enrollment, 40% of patients had locally advanced and 60% metastatic disease. All patients were evaluable for response and toxicity. On an intent-to-treat analysis, the overall response and disease control rates were 40 and 80 percent, respectively. The median progression-free survival was 6 months, and the median overall survival was 9 months. Major grade 3/4 toxicities were neutropenia (18 %), diarrhea (10 %) and hand-foot syndrome (8 %). There was no treatment-related death. It was concluded that the combination of gemcitabine with docetaxel and capecitabine is feasible and exhibits satisfactory degree of activity in patients with advanced pancreatic cancer, deserving further exploration [432].

There are limited data regarding the role of second-line treatment for metastatic pancreatic cancer (mPC) after the failure of initial chemotherapy. No data exist on the use of GTX after the failure of first-line therapy. It was identified patients who were given GTX chemotherapy for a diagnosis of mPC after the failure of initial therapy. Demographic features, progressionfree (PFS) and overall survival (OS), response to treatment, and toxicities were recorded. The 59 evaluable patients received a median of 2 prior therapies. Three had no prior gemcitabine. Median PS was 1. Median survival was 22 weeks; progression-free survival was 9.9 weeks. Survival did not correlate with the number of prior regimens but trended with PS. There were no radiologic responses; those with stable disease (n=21) had a better survival than those with progression (n=29) or unevaluable patients (n=9). Median survival was 38, 15, and 7 weeks, respectively. Grade 3 and 4 toxicities included leucopenia (n=14), anemia (n=7), and thrombocytopenia (n=6). Hospitalizations were required in 21 patients, for febrile neutropenia (n=7), non-neutropenic infection (n=3), pulmonary embolus (n=2), anemia or failure to thrive (n=9). A 75 percent drop or more in CA 19-9 correlated with improved survival. It was concluded that GTX is an active regimen in patients previously treated with gemcitabine for mPC. Better performance status and >75 percent drop in pretreatment CA 19-9 were associated with longer survival. The number of prior regimens did not predict for survival duration [433].

Studies treating adenocarcinoma of the pancreas with gemcitabine alone or in combination with a doublet have demonstrated modest improvements in survival. Recent reports have suggested that using the triple-drug regimen FOLFIRINOX can substantially extend survival in patients with metastatic disease. The authors were interested in determining the clinical benefit of another three-drug regimen of gemcitabine, docetaxel and capecitabine (GTX) in patients with advanced pancreatic adenocarcinoma. The cases of 154 patients, who received treatment with GTX chemotherapy with histologically confirmed locally advanced or metastatic pancreatic adenocarcinoma, were retrospectively reviewed. All demographic and clinical data were captured including prior therapy, adverse events, treatment response and survival. One hundred and seventeen metastatic and 37 locally advanced cases of adenocarcinoma of the pancreas were reviewed. Partial responses were noted in 11 percent of cases, and stable disease was observed in 62 percent of patients. Responses significantly correlated with toxicity (neutropenia, ALT elevation and hospitalizations). Grade 3 or greater hematologic and non-hematologic toxicities were noted in 41 percent and 9 percent of cases, respectively. Overall median survival was 12 months. Chemotherapy naïve patients with metastatic and locally advanced disease achieved a median survival of 11 and 25 months, respectively. It was observed a substantial survival benefit with GTX chemotherapy in the cohort of patients with advanced pancreatic cancer [434].

Gemcitabine and capcitabine plus docetaxel (PDXG) or epirubicne (PEXG)

PEFG regimen (P:cisplatin, E:epirubicin, F:5-fluorouracil, G:gemcitabine) significantly prolonged progression-free (PFS) and overall survival (OS) of patients with advanced pancreatic adenocarcinoma (PA) with respect to standard gemcitabine. The current trial was aimed at assessing whether the replacement of E with docetaxel (D) may improve 6 months PFS (PFS6). Chemo-naive patients with stage III or metastatic PA received P (30 mg/m(2) day 1 and 15), G (800 mg/m² day 1 and 15), and capecitabine (1,250 mg/m²/day days 1-28, without a break) and were randomized to receive either D at 25-30 mg/m² day 1 and 15 (arm A: PDXG regimen) or E at 30 mg/m² day 1 and 15 (arm B: PEXG regimen). Cycles were repeated every 28 days for a maximum of 6 months. The Fleming design was used to calculate the sample size on the probability of being PFS6. Assuming P0 40 percent and P1 60 percent, alpha = 0.05 and beta = 0.10; the study was to enroll 52 patients per arm. Between 2005 and 2008, 105 patients were enrolled, stratified by stage and randomized. Patients' characteristics were (A/B) the following: median age 61/59, PS >70 92/88 percent, metastatic disease 66/65 percent. PFS6 was 58 percent, and median OS was 11 months in both arms. A partial response was observed in 60/37 percent of patients. Main per cycle G3-4 toxicity was the following: neutropenia 4/13 percent, thrombocytopenia 2/4 percent, anemia 4/4 percent, and fatigue 6/3 percent. The inclusion of D instead of E yielded more objective response and less G3-4 neutropenia but did not improve PFS and OS. The present trial confirms the relevant impact on outcome of advanced PA of 4-drug regimens [435].

Gemcitabine, cisplatin and erlotinib (GPT)

Gemcitabine has been recognized as a standard chemotherapy in advanced pancreas cancer (APC). It was conducted a phase II study of a triple combination regimen (GPT) consisting of gemcitabine (G), cisplatin (P) and erlotinib (T) in patients with APC. Chemotherapy-naïve patients with locally advanced or metastatic, histologically confirmed adenocarcinoma of the pancreas were treated with erlotinib 100 mg daily, 1,000 mg/m² of gemcitabine and 25 mg/m² of cisplatin administered on days 1 and 8, respectively, every 3 weeks. The primary end point was objective response. Secondary end points included progression-free survival, overall survival and toxicity. The study was designed according to the optimal two-stage design. Twenty-two patients were enrolled between 2009 and 2010. No complete response was achieved and partial response was observed in 5 patients (26 %), stable disease in 7 (37 %), and progressive disease in 7 (37 %). The median time to progression was 4 months (95 % confidence interval 3 to 5 months), and the median overall survival 7 months (95 % confidence interval 4 to 10 months). The response rate in stage I reached the target (\geq 3/22, p0 10 %) established for movement to stage II but this study was determined to close earlier than planned because of unexpected treatment-related deaths (3 patients). It was concluded that the triple regimen of GPT is effective for APC. Treatmentrelated mortalities factored early closure of this GPT protocol. Considering effect and toxicity, this triple regimen seems to offer few benefits to the patients compared with gemcitabinebased doublets [436].

FOLFIRINOX

In the past 15 years, there have been seen few therapeutic advances for patients with pancreatic cancer, which is the fourth leading cause of cancer-related death in the United States. Currently, only about 6 percent of patients with advanced disease respond to standard gemcitabine therapy, and median survival is only about 6 months. Moreover, phase III trials have shown that adding various cytotoxic and targeted chemotherapeutic agents to gemcitabine has failed to improve overall survival, except in cases in which gemcitabine combined with erlotinib show minimal survival benefit. Several meta-analyses have shown that the combination of gemcitabine with either a platinum analog or capecitabine may lead

to clinically relevant survival prolongation, especially for patients with good performance status. Meanwhile, many studies have focused on the pharmacokinetic modulation of gemcitabine by fixed-dose administration, and metabolic or transport enzymes related to the response and toxicity of gemcitabine. Strikingly, a phase III trial in 2010 showed that, in comparison to gemcitabine alone, the FOLFIRINOX regimen in patients with advanced disease and good performance status, produced better median overall survival, median progression-free survival, and objective response rates. This regimen also resulted in greater, albeit manageable toxicity [437].

Gemcitabine, oxaliplatin, 5FU and conformal radiotherapy

Locally advanced inoperable pancreatic cancer (LAPC) has a poor prognosis. By increasing intensity of systemic therapy combined with an established safe chemoradiation technique, our intention was to enhance the outcomes of LAPC. In preparation for phase III evaluation, the feasibility and efficacy of our candidate regimen gemcitabine-oxaliplatin chemotherapy with sandwich 5-fluorouracil (5FU) and three-dimensional conformal radiotherapy (3DCRT) needs to be established. A total of 48 patients with inoperable LAPC without metastases were given gemcitabine (1000 mg/m² d1 + d15 q28) and oxaliplatin (100 mg/m² d2 + d16 q28) in induction (one cycle) and consolidation (three cycles), and 5FU 200 mg/m² per day over 6 weeks during 3DCRT 54 Gy. Median duration of sustained local control (LC) was 16 months, progression-free survival (PFS) was 11 months, and overall survival was 16 months. Survival rates for 1, 2, and 3 years were 70, 21, and 13 percent, respectively. Global quality of life did not significantly decline from baseline during treatment, which was associated with modest treatment-related toxicity. Fixed-dose gemcitabine and oxaliplatin, combined with an effective and safe regimen of 5FU and 3DCRT radiotherapy, was feasible and reasonably tolerated. The observed improved duration of LC and PFS with more intensive therapy over previous trials may be due to patient selection, but suggest that further evaluation in phase III trials is warranted [438].

Bevacizumab

Posterior reversible encephalopathy syndrome (PRES) is a potentially devastating complication of bevacizumab treatment. It was examined the clinical features, treatment and outcomes of patients who developed PRES following bevacizumab treatment at our institution and those reported in the literature. Patients were identified from the Mayo Clinic database and the published literature using PubMed and OVID databases, from 2006 to 2010, who developed PRES features within 3 weeks of bevacizumab treatment, who had brain imaging findings of focal vasogenic edema and radiologic proof of reversibility. Two patients with definite PRES were identified from our institution and a further 10 cases were identified from the published literature (total, n=12). The mean age of these patients was 52 years (range 4-68 years), four of whom were men and eight women. Headaches (n=7), seizures (n=6), visual disturbances (n=5) and nausea and vomiting (n=3) were the common presenting symptoms. In a majority of patients (n=10), an increase in blood pressure from their baseline values was observed during their acute presentation. PRES resolved following withdrawal of bevacizumab and blood pressure control in all patients. PRES is a catastrophic neurological complication of bevacizumab treatment, which responds favorably to prompt bevacizumab withdrawal and blood pressure control [439].

Erlotinib

A retrospective study examined pancreatic cancer patients who received combination gemcitabine and erlotinib to determine if the association between rash and outcomes observed in clinical trials would be observed in 'real-world' community oncology settings. Medical records from 10 community oncology practices were used to identify eligible

patients. Rash severity was classified as High (moderate/severe) versus Low (absent/mild) based on medical record review. Kaplan-Meier analysis assessed progression-free survival (PFS) and overall survival (OS) by rash status from a landmark of 42 days after treatment initiation. Cox regression with time-varying covariates tested whether high-severity rash predicted longer OS and PFS.The High Severity group (n=34) had significantly longer median OS from the landmark than the Low Severity group (n=134) (8 months vs 5 months). Cox regression analysis (n=174) confirmed a reduced risk of death with High Rash Severity (hazard ratio, HR, 0.67). Progression-free survival results showed a similar pattern (median PFS 2.4 months from landmark versus 2.0 months for High vs Low Severity groups. Results from this community sample were consistent with findings from randomized clinical trials, showing that longer OS is predicted by high-severity rash in erlotinib-treated pancreatic cancer patients [440].

Guggulstrone and gemcitabine

Guggulsterone is a dietary plant sterone possessing therapeutic potential against cancers. However, the antitumor effect of this natural compound on pancreatic cancer has not been determined yet. One study was designed to investigate the therapeutic efficacy of guggulsterone in pancreatic cancer. In the study, it was examined the effect of guggulsterone on cell proliferation and apoptosis in pancreatic cancer cell lines, and then, it was investigated the mechanisms responsible for the effect of guggulsterone. Finally, it was investigated whether the combination of guggulsterone and gemcitabine had an additional therapeutic effect compared to gemcitabine single regimen in pancreatic cancer cell lines (in vitro) and in a xenograft model using nude mice (in vivo). In vitro, the combination treatment resulted in more growth inhibition and apoptosis through the down-regulation of nuclear factor KB activity with suppression of Akt and BcL-2 and through the activation of c-Jun NH2terminal kinase and Bax in pancreatic cancer cell lines. In vivo, the combination therapy augmented tumor growth inhibition through the same mechanisms in tumor tissue. The combination of guggulsterone to gemcitabine enhanced antitumor efficacy through apoptosis induction by suppressing Akt and nuclear factor kappaB activity and by modulating apoptosis-related protein expression in pancreatic cancer [441].

G17DT

One study aimed to investigate G17DT, an immunogen producing neutralizing antibodies against the tumor growth factors amidated and glycine-extended forms of gastrin-17, in the treatment of pancreatic cancer. A randomized, double-blind, placebo-controlled, groupsequential multicenter trial of G17DT in patients with advanced pancreatic cancer unsuitable for or unwilling to take chemotherapy. Inclusion criteria were a Karnofsky performance score of 60 or higher and a life expectancy of more than 2 months. Patients received G17DT or placebo emulsion at weeks 0, 1, 3, 24, and 52. The primary end point was survival, and secondary end points were tolerability, Karnofsky performance. A total of 154 patients were recruited: 79 G17DT and 75 placebo. A final analysis of the intention-to-treat population, using a proportional hazards model, stratifying by disease stage and adjusting for interim analysis, gave a hazard ratio for mortality of 0.75 (95 % confidence interval, 0.51 to 1.10, G17DT/placebo). A conventional analysis without adjustment for disease stage or interim analysis, censoring for chemotherapy and excluding protocol violators, gave median survival periods of 151 (G17DT) and 82 days (placebo) (log-rank test). Patients developing anti-G17DT responses (74 %) survived longer than nonresponders or those on placebo (median survival, 176 vs 63 vs 83). G17DT was well tolerated [442].

Triptolide

It was aimed to pharmacologically downregulate heat shock protein 27 (HSP27) through triptolide (TPL) to improve the drug sensitivity of pancreatic cancer to cisplatin (DDP). In vitro, it was assessed cell viability and apoptosis by the combination of TPL and DDP in gemcitabine-resistant human pancreatic carcinoma PANC-1 and MIA PaCa-2 cell lines and examined the effect of silencing HSP27 by a small interfering RNA on cytotoxicity induced by TPL or DDP. In vivo, we apply TPL with DDP in a xenograft model to test the synergic action. Triptolide cooperates with DDP to decrease cell viability and to induce apoptosis via the mitochondrial pathway, which is accompanied by a sharp decline in HSP27. Knocking down endogenous HSP27 can sensitize cancer cells to cytotoxicity with TPL or DDP, indicating the critical role of HSP27 down-regulation in the synergic effect. Meanwhile, TPL acts in synergy with DDP to cause tumor regression in vivo. Thus, the combined therapy of TPL and DDP triggers a synergic apoptosis via inhibiting HSP27 in human gemcitabine-resistant pancreatic carcinoma and has a strong potential to be developed into a new effective regimen for pancreatic cancer treatment [443].

Drugdelivery by nanotechnology

Cancers of the upper GI tract, liver and pancreas have some of the poorest prognoses of any malignancies. Advances in diagnosis and treatment are sorely needed to improve the outcomes of patients. Nanotechnology offers the potential for constructing tailor-made therapies capable of targeting specific cancers. The particles themselves may be endowed with multifunctional properties that can be exploited for both diagnosis and treatment. Although development of therapies is still in the early stages, the use of nanoparticles (NPs) is widespread in diagnostic applications and will probably involve all areas of medicine in the future. Research into NPs is ongoing for upper gastrointestinal, liver and pancreatic cancers, and their use is becoming increasingly popular as contrast media for radiological investigations. Although more sophisticated technologies capable of active targeting are still in the early stages of assessment for clinical use, a small number of NP-based therapies are in clinical use4].

Second line therapy

The role of salvage chemotherapy after first-line therapy in advanced pancreatic cancer has not yet been established. It was intended to identify prognostic factors for long-term survival of advanced pancreatic adenocarcinoma patients with second-line chemotherapy and to devise a prognostic model of clinical parameters. It was analysed 90 patients who had received second-line chemotherapy after the failure of first-line therapy in recurrent or metastatic pancreatic adenocarcinoma between 2003 and 2008. The median age at the time of second-line chemotherapy was 62 years (range 40-75) and the median Eastern Cooperative Oncology Group (ECOG) performance status was 1 (0-2). Median progressionfree survival and overall survival for second-line chemotherapy were 2 and 5 months, respectively, with an overall response rate of 10 percent. In multivariate analysis, an ECOG performance status of 2 or more, non-responder for first-line chemotherapy and albumin level of <3.5mg/dl were independent prognostic factors for decreased overall survival for all 90 patients. Overall survival was estimated based on the number of adverse prognostic factors: zero or one (good prognostic group), two (intermediate group) or three (poor prognostic group). The median overall survival for good (n=50), intermediate (n=24) and poor (n=16) prognostic groups was 6, 3 and 2 months, respectively. The result suggests that second-line chemotherapy may be beneficial for overall survival in patients with ECOG performance status 0-1, albumin level \geq 3.5mg/dl and response to first-line chemotherapy [445].

Experimental

Cetuximab plus trastuzumab

It was previously demonstrated the synergistic therapeutic effect of the cetuximab (antiepidermal growth factor receptor, EGFR, monoclonal antibody, mAb)-trastuzumab (anti-HER2 mAb) combination (2mAbs therapy) in HER2(low) human pancreatic carcinoma xenografts. Here, it was compared the 2mAbs therapy, the erlotinib (EGFR tyrosine kinase inhibitor, TKI)-trastuzumab combination and lapatinib alone (dual HER2/EGFR TKI) and explored their possible mechanisms of action. The effects on tumor growth and animal survival of the three therapies were assessed in nude mice xenografted with the human pancreatic carcinoma cell lines Capan-1 and BxPC-3. After therapy, EGFR and HER2 expression and AKT phosphorylation in tumor cells were analyzed by Western blot analysis. EGFR/HER2 heterodimerization was quantified in BxPC-3 cells by time-resolved FRET. In Kras-mutated Capan-1 xenografts, the 2mAbs therapy gave significantly higher inhibition of tumor growth than the erlotinib/trastuzumab combination, whereas in BxPC-3 (wild-type Kras) xenografts, the erlotinib/trastuzumab combination showed similar growth inhibition but fewer tumor-free mice. Lapatinib showed no antitumor effect in both types of xenografts. The efficacy of the 2mAbs therapy was partly Fc-independent because F(ab')(2) fragments of the two mAbs significantly inhibited BxPC-3 growth, although with a time-limited therapeutic effect. The 2mAbs therapy was associated with a reduction of EGFR and HER2 expression and AKT phosphorylation. BxPC-3 cells preincubated with the two mAbs showed 50% less EGFR/HER2 heterodimers than controls. In pancreatic carcinoma xenografts, the 2mAbs therapy is more effective than treatments involving dual EGFR/HER2 TKIs. The mechanism of action may involve decreased AKT phosphorylation and/or disruption of EGFR/HER2 heterodimerization [446].

Radiotherapy

Pancreatic cancer remains associated with an extremely poor prognosis. Surgical resection can be curative, but the majority of patients present with locally advanced or metastatic disease. Treatment for patients with locally advanced disease is controversial. Therapeutic options include systemic therapy alone, concurrent chemoradiation, or induction chemotherapy followed by chemoradiation. It was reviewed the evidence to date regarding the treatment of locally advanced pancreatic cancer (LAPC), as well as evolving strategies including the emerging role of targeted therapies. It was proposed that if radiation is used for patients with LAPC, it should be delivered with concurrent chemotherapy and following a period of induction chemotherapy [447].

Radiotherapy planning

To develop contouring guidelines to be used in the Radiation Therapy Oncology Group protocol 0848, a phase III randomized trial evaluating the benefit of adjuvant chemoradiation in patients with resected head of pancreas cancer. A consensus committee of six radiation oncologists with expertise in gastrointestinal radiotherapy developed stepwise contouring guidelines and an atlas for the delineation of the clinical target volume (CTV) in the postoperative treatment of pancreas cancer, based on identifiable regions of interest and margin expansions. Areas at risk for subclinical disease to be included in the CTV were defined, including nodal regions, anastomoses, and the preoperative primary tumor location. Regions of interest that could be reproducibly contoured on postoperative imaging after a pancreaticoduodenectomy were identified. Standardized expansion margins to encompass areas at risk were developed after multiple iterations to determine the optimal margin expansions. New contouring recommendations based on CT anatomy were established. Written guidelines for the delineation of the postoperative CTV and normal tissues, as well as

a Web-based atlas, were developed. These new guidelines will help physicians create fields that better encompass areas at risk and minimize dose to normal tissues [448].

To indentify effective methods to address the large interfractional variations for pancreas irradiation, it was compared various used/proposed online strategies. The daily CTs acquired using a respiration-gated in-room CT for 9 pancreatic cancer patients treated with IGRT (i.e. online repositioning based on rigid-body alignment) were analyzed. The contours of the pancreas and duodenum on each daily CT set were generated by populating those from the planning CT using a deformable registration tool (ABAS, Elekta) with manual editing. PTV was generated with 3 mm margin. Nine online strategies were considered: 1) IGRT with 0 mm additional margin, 2) IGRT with 2mm AM, 3) IGRT with 5mm AM, 4) IGRT with plan renormalized to maintain 95 percent PTV coverage, 5) Full scale reoptimization. 6) Reoptimization starting from the original plan, 7) Segment Aperture Morphing (SAM) from the original plan based on PTV shape change 8) SAM plus Segment Weight Optimization (SWO), 9) Reoptimization starting from the SAM plan. One way ANOVA (analysis of variance) was applied to plan qualities for the 9 strategies to assess statistical significance in difference. The standard IGRT strategies (1-3) resulted in either inadequate PTV coverage or higher duodenum doses. Margin expansion along is not efficient to account for the changes. Full-scale reoptimization resulted in the best plan but requiring delineation of several structures. Reoptimization on top of available plan (strategies 6 and 9) was considerably faster. SAM strategy (7) is the fastest online replanning, as it requires only one structure (target) delineation, and its plan quality was comparable to that for the full-scale reoptimization. It was concluded that online replanning strategies can lead to either reduced duodenum dose or improved target coverage as compared to the current practice of IGRT. The SAM-based online replanning is comparable to the full scale reoptimization and is efficient for practical use [449].

Due to lack of soft-tissue contrast, target distortion for the upper-abdomen targets such as pancreatic tumors is complicated and requiring sufficient remedy. By applying automatic contour propagation, the authors use the information obtained from 4D CT to test if the deformable image registration compensates the respiration-induced distortion of pancreatic tumor in free breathing (FB) CT images. Ten patients with unresected pancreatic cancer treated with either preoperative or definitive chemoradiation were studied. Pancreas GTVs were delineated on the FB CT. Using deformable image registration, the FB GTV contours were propagated to each phase of the 4D CT images taken right after the FB CT, and were compared with the FB GTV to see difference in tumor volume and tumor size along individual dimensions. A one-dimensional tumor motion in proportion to $\cos 4(\omega t)$ was simulated to calculate the probability distribution function for different magnitude of distortions during FB CT scans, and a binary classification test was conducted to analyze the observed results. Results: The probability distribution function predicted that four out of the ten cases would have substantial target distortion given the variation in target motion amplitudes. Three of these four cases show substantial difference in the superior-inferior size of FB GTV compared to the average 4D GTV, taking into account the uncertainties caused by motions perpendicular to the scanning axis and resolution of the CT scanner. The binary classification test yielded a precision of 75 percent and an accuracy of 90 percent. Thus, pancreatic GTV distorted due to respiration-induced tumor motion is effectively compensated by contour propagation from free-breathing CT to 4D CT using DIR. Union of GTVs of all breathing phases or IGTV can be genreated from 4D set of GTVs propagated from that of free breathing [450].

Radiotherapy is widely used in the treatment of pancreatic cancer. Currently, recommendation has been given for the delineation of the clinical target volume (CTV) in adjuvant radiotherapy. Although there is no consensus concerning the elective nodal irradiation (ENI) in pancreatic cancer RT, it could be justified in a treatment with curative intent. Moreover, a high frequency of lymphatic spread (60-80 %) was reported in head

pancreatic cancer and a high rate of local and nodal failure was noted in pathologic and clinical analyses (up to 75%). Based on these data, the prognosis of these patients could be theoretically improved reaching a higher local control and reducing the nodal recurrence rate, as already shown in resectable pancreatic carcinoma treated with ENI and concurrent chemotherapy (local recurrence rate with or without ENI: 0-13 % vs 25 %, respectively). Nevertheless, the close presence of organs at risk (OARs) such as kidneys, liver, small bowel, stomach, duodenum and spinal cord remain the main problems of abdominal radiotherapy, especially when large volume is treated. Therefore, CT-based definition of the clinical target volume (CTV) and 3D treatment planning (3D-CRT), thus reducing the dose to OARs, is strongly recommended and is currently considered the standard approach. Further advantages can be achieved by intensity modulated radiotherapy (IMRT), as well as by 4D treatment planning. For both 3D and IMRT treatment planning, a proper knowledge, definition and delineation of CTV is required. Moreover, this issue became particularly relevant for IMRT-based treatment planning based on the dose gradients close to the planning target volume (PTV). For this reason, standardized contouring guidelines to ensure the adequacy of the CTV should be provided. Currently, no recommendations based on modern imaging modalities are available for preoperative or definitive RT. Moreover, several anatomic and pathologic studies have been conducted to identify lymphatic network and high risk areas of lymph node involvement and to define the pattern of perineural invasion of pancreatic cancer. Concerning lymphatic drainage, a rich communication between the anterior surface of the head of the pancreas, the common hepatic artery, the celiac trunk origin and the superior mesenteric artery was described. As well as a lymphatic pathway from the body and the tail of pancreas was shown around the splenic blood vessels and the inferior pancreatic artery up to the lymph nodes situated on the left side of the celiac trunk and the superior mesenteric artery. The extent of perineural invasion has been also demonstrated in a number of pathologic studies, often showing lymphatic emboli and neural invasions in the soft tissue adherent to the vessels and near to the metastatic nodes. The close embryologic development relationship of lymphatic and nervous structures could justify the dual pathway of dissemination of pancreatic cancer along peripancreatic connective tissues. In particular, a review of 18 pathologic reports (reported on 5954 resectable pancreatic cancer patients treated with radical surgery) was recently conducted to evaluate the probability of lymph node metastases and to define the high risk lymph nodal regions, related to the primary tumor site (head or body/tail of pancreas). Based on these reviewed pathologic data, the aim of one study was to propose criteria for CTV definition and delineation including ENI in the preoperative or exclusive treatment of pancreatic cancer. The aim of the investigation was to propose standard criteria for the CTV definition and delineation in the preoperative or exclusive treatment of pancreatic cancer, with particular attention to elective lymph node areas. It must be admitted that ENI is controversial and may be considered questionable. In fact, palliative RT has been shown to be effective even without prophylactive nodal irradiation. Furthermore, in order to increase the resectability, a dose escalation to the gross tumor volume (GTV) more than a prophylactic dose may be required, as well as the inclusion of lymph nodes in the irradiated volume may be associated with increased toxicity and represent a limit for concurrent chemotherapy. Guidelines for the delineation of ENI were proposed by Brunner et al but concerned only the treatment of head pancreatic carcinoma. Based on pathologic evaluation of 175 patients with ductal head pancreatic carcinoma who underwent radical pancreatoduodenectomy, the study confirmed the high probability of lymphatic spread and the need of the elective irradiation of regional and paraaortic lymphatic areas. Indeed, the total incidence of regional lymph node metastasis was 76 percent (133/175 cases) and the posterior pancreaticoduodenal area, superior and inferior pancreatic head margin, anterior pancreaticoduodenal area, hepatoduodenal ligament, superior pancreatic body and superior mesenteric artery were identified as high-risk lymphatic involvement areas and selected for elective treatment. It was considered the 3 percent cut-off value appropriate. Moreover, if a "classical" cut off of 10-15 percent was chosen, some commonly considered high risk lymph node areas in postoperative setting (as common hepatic artery lymph nodes, hepatoduodenal ligament lymph

nodes, celiac trunk lymph nodes, paraaortic lymph nodes for head tumors and hilus of the spleen lymph nodes for body/tail tumors) would been excluded. A 10 mm margin was added around the arteries to define the lymphatic area, according to pathologic studies, where tumor infiltration was demonstrated in the soft tissue area with lymphatic and neural plexus, 10 mm around the artery. Furthermore, previous guidelines for pelvic lymph nodes delineation using IMRT, showed the possibility to cover 94 percent of nodes using a 10 mm margin around arteries. Looking at these criteria, for tumors located in the head of the pancreas, it was proposed the inclusion in the elective CTV of the following nodal areas: the infrapyloric lymph nodes (Group 6), the lymph nodes around the common hepatic (Group 8) and the hepatoduodenal ligament (Group 12), the celiac trunk lymph nodes (Group 9), the posterior pancreatico-duodenal lymph nodes (Group 13), the superior mesenteric lymph (Group 14), the paraaortic lymph nodes (Group 16) and the anterior nodes pancreaticoduodenal lymph nodes (Group 17). For patients with pancreatic body and tail disease, it was included the lymph nodes around the common hepatic artery (Group 8), the celiac trunk (Group 9), the splenic artery and the ilus of spleen (Group 10 and 11), the hepatoduodenal ligament (Group 12), the superior mesenteric artery (Group 14), the paraaortic region (Group 16), and the inferior body area (Group 18). It was thus proposed a set of guidelines for elective treatment of high-risk nodal areas and CTV delineation. Reference CT images were provided. The proposed guidelines could be used for preoperative or definitive radiotherapy (RT) for carcinoma of the head and body of the pancreas. Further clinical investigations are needed to validate the defined CTVs [451].

Dosimetry

To experimentally investigate the effects of variations in respiratory motion during breathholding (BH) at end-exhalation (EE) on intensity-modulated radiotherapy (BH-IMRT) dose distribution using a motor-driven base, films, and an ionization chamber a study was done. Measurements were performed on a linear accelerator, which has a 120-leaf independently moving multileaf collimator with 5-mm leaf width at the isocenter for the 20-cm central field. Polystyrene phantoms with dimensions of 40 \times 40 \times 10 cm were set on a motor-driven base. All gantry angles of seven IMRT plans (a total of 35 fields) were changed to zero, and doses were then delivered to a film placed at a depth of 4 cm and an ionization chamber at a depth of 5 cm in the phantom with a dose rate of 600 MU/min under the following conditions: pulsation from the abdominal aorta and baseline drift with speeds of 0.2 mm/s (BD(0.2mm/s)) and 0.4 mm/s (BD(0.4mm/s)). As a reference for comparison, doses were also delivered to the chamber and film under stationary conditions. In chamber measurements, means ± standard deviations of the dose deviations between stationary and moving conditions were 0.52 ± 1.03 percent -0.07 \pm 1.21 percent, and 0.03 \pm 1.70 percent for pulsation, BD(0.2mm/s), and BD(0.4mm/s), respectively. In the case of BD(0.4mm/s), the y passing rate for four of 35 fields (11.4 %) did not reach 90 percent with a criterion of 3 percent/3 mm. This study suggested that the baseline drift of >5 mm should be avoided in the BH-IMRT [452].

To quantitatively characterize interfractional anatomic variations in pancreatic cancer radiotherapy (RT) and to study dosimetric advantages for using an online adaptive replanning scheme to account for these variations. Targets and organs at risk (OAR) were delineated by autosegmentation based on daily computed tomography (CT) images acquired using a respiration-gated in-room CT during daily image-guided RT (IGRT) for 10 pancreatic cancer patients. Various parameters, including the maximum overlap ratio (MOR) between the volumes based on planning and daily CTs for a structure, while the overlapping volumes were maximized, were used to quantify the interfractional organ deformation with the intrafractional variations largely excluded. An online adaptive RT (ART) was applied to these daily CTs. To evaluate the dosimetric benefits of ART, the dose distributions from the online ART were compared to those from the repositioning in the current standard IGRT practice. The interfractional anatomic variations, particularly the organ deformation, are significant

during pancreas irradiation. For the patients studied, the average MORs of all daily CTs were 80 percent, 62 percent, and 72 percent for pancreatic head, duodenum, and stomach, respectively. The online ART leads to improved dosimetric plan with better target coverage and/or OAR sparing than IGRT repositioning. For the patients studied, the mean V (50.4 Gy) (volume covered by 50.4 Gy) for the duodenum was reduced from 43 percent for IGRT to 16 percent for the online ART scheme. It was concluded that the online adaptive RT scheme can effectively account for the significant interfractional anatomic variations observed in pancreas irradiation. The dosimetric advantages with the online ART may enable safe dose escalation in radiation therapy for pancreatic cancer [453].

Tumor volume as predictor of effect

It was assessed whether gross tumor volume (GTV) determined by fusion of contrastenhanced computerized tomography (CT) and 18F-fluoro-deoxy-D-glucose positron emission tomography-CT (FDG-PET-CT) based radiotherapy planning could predict outcomes, namely overall survival (OS), local-regional progression-free survival (LRPFS), and progression-free survival (PFS) in cases with locally advanced pancreas cancer (LAPC) treated with definitive concurrent chemoradiotherapy. A total of 30 patients with histological proof of LAPC underwent 50.4 Gy (1.8 Gy/28 fractions) of radiotherapy concurrent with continuously infused 5-FU followed by 4 to 6 courses of maintenance gemcitabine. Target volume delineations were performed on FDG-PET-CT-based RTP. Patients were stratified into 2 groups: GTV lesser (GTVL) versus greater (GTVG) than cut off value determined by receiver operating characteristic (ROC) analysis, and compared in terms of OS, LRPFS and PFS. Median GTV delineated according to the FDG-PET-CT data was 100 cm³. Cut off GTV value determined from ROC curves was 91 cm³. At a median follow up of 11 months, median OS, LRPFS and PFS for the entire population were 10, 8 and 6 months, respectively. Median OS, LRPFS and PFS for GTVL and GTVG cohorts were 16 vs 10, 11 vs 6, and 9 vs 5 months, respectively. It was concluded that the superior OS, LRPFS and PFS observed in GTVL patients over GTVG ones suggests a potential for FDG-PET-CT-defined GTV size in predicting outcomes of LAPC patients treated with definitive C-CRT, which needs to be validated by further studies with larger cohorts [454].

Adjuvant proton therapy

To determine the potential role for adjuvant proton-based radiotherapy (PT) for resected pancreatic head cancer 8 consecutive patients with resected pancreatic head cancers underwent optimized intensity-modulated radiotherapy (IMRT) treatment planning during 2008,. IMRT plans used between 10 and 18 fields and delivered 45 Gy to the initial planning target volume (PTV) and a 5.4 Gy boost to a reduced PTV. PTVs were defined according to the Radiation Therapy Oncology Group 9704 radiotherapy guidelines. Ninety-five percent of PTVs received 100 percent of the target dose and 100 percent of the PTVs received 95 percent of the target dose. Normal tissue constraints were as follows: right kidney V18 Gy to <70 percent; left kidney V18 Gy to <30 percent; small bowel/stomach V20 Gy to <50 percent, V45 Gy to <15 percent, V50 Gy to <10 percent, and V54 Gy to <5 percent; liver V30 Gy to <60 percent; and spinal cord maximum to 46 Gy. Optimized two- to three-field threedimensional conformal proton plans were retrospectively generated on the same patients. The team generating the proton plans was blinded to the dose distributions achieved by the IMRT plans. The IMRT and proton plans were then compared. All proton plans met all normal tissue constraints and were isoeffective with the corresponding IMRT plans in terms of PTV coverage. The proton plans offered significantly reduced normal-tissue exposure over the IMRT plans with respect to the following: median small bowel V20 Gy, 15 percent with protons versus 47 percent with IMRT; median gastric V20 Gy, 2 percent with protons versus 20 percent with IMRT; and median right kidney V18 Gy, 27 percent with protons versus 50 percent with IMRT. It was concluded that by reducing small bowel and stomach exposure, protons have the potential to reduce the acute and late toxicities of postoperative chemoradiation in this setting [455].

Stereotactic body radiation therapy

Local control rates are poor in the treatment of pancreatic cancer. Although conventional radiation techniques may be employed for local control, they incur toxicity and interrupt use of full dose gemcitabine, the most active systemic agent for the disease. Radiation doses are limited by the presence of critical normal structures, which include spinal cord, small bowel, stomach and kidneys. The emerging technology of stereotactic body radiation therapy (SBRT), as an adjunct or alternative to conventional radiation techniques, offers the potential for radiation dose escalation, retreatment, and/or decreased interruption of systemic therapy. The safety, efficacy and technical aspects of this treatment modality have not been fully defined, and the role of radiotherapy is controversial in both the adjuvant (postoperative) and definitive (unresectable localized disease) settings. Supporters of adjuvant radiotherapy point to the landmark Gastrointestinal Tumor Study Group (GITSG) study, where a survival benefit was demonstrated with the addition of adjuvant chemoradiation and maintenance chemotherapy versus surgery alone. Detractors of adjuvant radiotherapy counter with the apparent detrimental effect of chemoradiation from the European Study Group for Pancreatic Cancer (ESPAC-1). The underpowered European Organization for Research and Treatment of Cancer (EORTC) trial has been interpreted as both undermining the role of adjuvant radiation therapy and supporting it. It was investigated the role of hypofractionated stereotactic body radiation therapy (SBRT) for salvage or boost treatment after conventional doses of external beam radiation therapy. All patients treated with SBRT for pancreatic adenocarcinoma from 2002 through 2007 were examined. Eligible patients had prior external beam radiation therapy to the pancreas. Treatment parameters and clinical and radiographic follow-up were evaluated. Twenty-eight patients were identified who received SBRT after a median prior external beam radiotherapy dose of 50.4 Gy. The median patient age was 63 years old and the median follow-up was 6 months. Twelve of fourteen (86 %) evaluable patients were free from local progression, with three partial responses and nine patients with stable disease. Toxicity consisted of one case of acute Grade II nausea/vomiting, and two cases of Grade III late GI toxicity. The median overall survival was 6 months, with 18 percent survival and 70 percent freedom from local progression at one year. It was concluded that hypofractionated SBRT reirradiation of localized pancreatic cancer is a well-tolerated treatment. Reirradiation is a clinically relevant subject of investigation given that approximately one fourth of all patients who undergo optimal trimodality therapy suffer from local failure. For patients with residual or recurrent localized disease after definitive treatment, current treatment options are limited. Response rates are poor with chemotherapy alone and surgical resection is possible in only highly selected cases. Though patients also have significant risk for development of regional or distant disease, local progression may cause significant morbidity. SBRT has been shown to provide excellent local control rates when used in the definitive setting. The minimal toxicity and short treatment duration of SBRT allow for the early resumption of systemic chemotherapy. However, interpretation of local control is limited by the patients lost to radiographic follow-up, the difficulty of interpreting CT findings, and short follow-up secondary to distant progression and patient mortality. A disparity exists in the reported toxicities for SBRT. The Pittsburgh, Beth Israel, and Stanford single SBRT alone and boost trials suggest grade III and higher toxicities are less than 10-15 percent with SBRT. A Danish study and Stanford SBRT with gemcitabine study suggest significantly higher rates of toxicity. The current series suggests that with modest hypofractionation of SBRT (3-5 fractions) to limited volumes treatment can be delivered with acceptable acute and late GI toxicity (less than 10 %) in the setting of prior chemotherapy and definitive doses of external beam radiotherapy [456].

Stereotactic body radiation therapy (SBRT) has emerged as a potential treatment option for local tumor control of primary malignancies of the pancreas. It was reported the experience with SBRT in patients with pancreatic adenocarcinoma who were found not to be candidates for surgical resection. The prospective database of the first 20 consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor under an IRB approved protocol was reviewed. Prior to SBRT, cylindrical solid gold fiducial markers were placed within or around the tumor endoscopically (n=13), surgically (n=4), or percutaneously under computerized tomography (CT)-guidance (n=3) to allow for tracking of tumor during therapy. Mean radiation dose was 25 Gray (Gy) (range 22-30 Gy) delivered over 1-3 fractions. Chemotherapy was given to 68 percent of patients in various schedules/timing. Patients had a mean gross tumor volume of 57 cm³ (range 10-118 cm³ before SBRT. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21 and 38 percent, respectively. Median follow-up was 15 months (range 5-23 months). The overall rate of freedom from local progression at 6 and 12 months were 88 and 65 percent. The probability of overall survival at 6 and 12 months were 89 and 56 percent. No patient had a complication related to fiducial markers placement regardless of modality. The rate of radiation-induced adverse events was: grade 1-2 (11 %) and grade 3 (16 %). There were no grade 4/5 adverse events seen. The preliminary results showed SBRT as a safe and likely effective local treatment modality for pancreatic primary malignancy with acceptable rate of adverse events [457].

Combined with gemcitabine and erlotinib

To determine the recommended dose of radiotherapy when combined with full-dose gemcitabine and erlotinib for unresected pancreas cancer patients with unresected pancreatic cancer (Zubrod performance status 0-2) were eligible for the present study. Gemcitabine was given weekly for 7 weeks (1,000 mg/m²) with erlotinib daily for 8 weeks (100 mg). A final toxicity assessment was performed in week 9. Radiotherapy (starting at 30 Gy in 2-Gy fractions, 5 d/wk) was given to the gross tumor plus a 1-cm margin starting with the first dose of gemcitabine. A standard 3 plus 3 dose escalation (an additional 4 Gy within 2 days for each dose level) was used, except for the starting dose level, which was scheduled to contain 6 patients. In general, Grade 3 or greater gastrointestinal toxicity was considered a dose-limiting toxicity, except for Grade 3 anorexia or Grade 3 fatigue alone. A total of 20 patients were treated (10 men and 10 women). Nausea, vomiting, and infection were significantly associated with the radiation dose. Of the 20 patients, 5 did not complete treatment and were not evaluable for dose-escalation purposes (3 who developed progressive disease during treatment and 2 who electively discontinued it). Dose-limiting toxicity occurred in none of 6 patients at 30 Gy, 2 of 6 at 34 Gy, and 1 of 3 patients at 38 Gy. The results of the present study have indicated that the recommended phase II dose is 30 Gy in 15 fractions [458].

Intensity-modulated radiotherapy (IMRT)

Intensity-modulated radiotherapy (IMRT) is increasingly incorporated into therapy for pancreatic cancer. A concern regarding this technique is the potential for geographic miss and decreased local control. It was analyzed patterns of first failure among patients treated with IMRT for resected pancreatic cancer. Seventy-one patients who underwent resection and adjuvant chemoradiation for pancreas cancer are included in this report. IMRT was used for all to a median dose of 50.4 Gy. Concurrent chemotherapy was 5-FU-based in 72 percent of patients and gemcitabine-based in 28 percent. At median follow-up of 24 months, 49/71 patients (69 %) had failed. The predominant failure pattern was distant metastases in 35/71 patients (49 %). The most common site of metastases was the liver. Fourteen patients (19 %) developed locoregional failure in the tumor bed alone in 5 patients, regional nodes in 4 patients, and concurrently with metastases in 5 patients. Median overall survival (OS) was 25

months. On univariate analysis, nodal status, margin status, postoperative CA 19-9 level, and weight loss during treatment were predictive for OS. On multivariate analysis, higher postoperative CA19-9 levels predicted for worse OS on a continuous basis. A trend to worse OS was seen among patients with more weight loss during therapy. Patients with positive nodes and positive margins also had significantly worse OS (HR for death 2.8 and 2.6, respectively). Grade 3-4 nausea and vomiting was seen in 8% of patients. Late complication of small bowel obstruction occurred in 4 (6 %) patients. It was the first comprehensive report of patterns of failure among patients treated with adjuvant IMRT for pancreas cancer. IMRT was not associated with an increase in local recurrences in our cohort. These data support the use of IMRT in the recently activated EORTC/US Intergroup/RTOG 0848 adjuvant pancreas trial [459].

The dose to an organ at risk (OAR) depends in large part on its orientation and distance to the planning target volume (PTV). To develop a model to assess the quality of an intensity modulated radiation therapy (IMRT) treatment plan using data of prior patients with pancreatic adenocarcinoma a database of 33 previously treated patients with pancreatic cancer was gueried to find patients with less favorable PTV-OAR configuration than a new case. The minimal achieved dose among the selected patients should also be achievable for the OAR of the new case. This way the achievable doses to the OARs of 25 randomly selected pancreas cancer patients were predicted. The patients were replanned to verify if the predicted dose could be achieved. The new plans were compared to their original clinical plans. The predicted doses were achieved within 1 and 2 Gy for more than 82 and 94 percent of the patients, respectively, and were a good approximation of the minimal achievable doses. The improvement after replanning was 1.4 Gy (range 0-4.6 Gy) and 1.7 Gy (range 0-6.3 Gy) for the mean dose to the liver and the kidneys, respectively, without compromising target coverage or increasing radiation dose to the bowel, cord or stomach. The model could accurately predict the achievable doses, leading to a considerable decrease in dose to the OARs and an increase in treatment planning efficiency [460].

It was reported the outcomes and toxicities in patients treated with intensity-modulated radiotherapy (IMRT) for pancreatic adenocarcinoma 47patients with pancreatic adenocarcinoma were treated with IMRT between 2003 and 2008. Of these 47 patients, 29 were treated adjuvantly and 18 definitively. All received concurrent 5-fluorouracil chemotherapy. The treatment plans were optimized such that 95 percent of the planning target volume received the prescription dose. The median delivered dose for the adjuvant and definitive patients was 50.4 and 54.0 Gy, respectively. The median age at diagnosis was 64 years. For adjuvant patients, the 1- and 2-year overall survival rate was 79 and 40 percent, respectively. The 1- and 2-year recurrence-free survival rate was 58 percent and 17 percent, respectively. The local-regional control rate at 1 and 2 years was 92 and 80 percent, respectively. For definitive patients, the 1-year overall survival, recurrence-free survival, and local-regional control rate was 24, 16, and 64 percent, respectively. Four patients developed Grade 3 or greater acute toxicity (9 %) and four developed Grade 3 late toxicity (9 %). It was concluded that a small percentage of adjuvant patients have durable disease control, and with improved therapies, this proportion will increase. Systemic therapy offers the greatest opportunity. The present results have demonstrated that IMRT is well tolerated. Compared with those who received three-dimensional conformal radiotherapy in previously reported prospective clinical trials, patients with pancreatic adenocarcinoma treated with IMRT in this series had improved acute toxicity [461].

Intratumoural treatment

It was developed (224)Ra-loaded wires that when inserted into solid tumors, release radioactive atoms that spread in the tumor and irradiate it effectively with alpha particles (diffusing alpha-emitters radiation therapy, DaRT). In one study, it was tested the ability of intratumoral (224)Ra-loaded wires to control the local growth of pancreatic tumors and the

enhancement of this effect by chemotherapy. Pancreatic mouse tumors (Panc02) were treated with (224)Ra-loaded wire(s) with or without gemcitabine. The tumor size and survival were monitored, and autoradiography was performed to evaluate the spread of radioactive atoms inside the tumor. Mouse and human pancreatic cancer cells, irradiated in vitro by alpha particles with or without chemotherapy, were evaluated for cell growth inhibition. The insertion of (224)Ra-loaded wires into pancreatic tumors in combination with gemcitabine achieved significant local control and was superior to each treatment alone. A dosimetric analysis showed the spread of radioactive atoms in the tumor around the wires. Alpha particles combined with gemcitabine or 5-FU killed mouse and human cells in vitro better than each treatment alone. DaRT in combination with gemcitabine was proven effective against pancreatic tumors in vivo and in vitro, and the process may be applicable as a palliative treatment for patients with pancreatic cancer [462].

Cost-effectiveness

Radiotherapy may improve the outcome of patients with pancreatic cancer but at an increased cost. In this study, the authors evaluated the cost-effectiveness of modern radiotherapy techniques in the treatment of locally advanced pancreatic cancer. A Markov decision-analytic model was constructed to compare the cost-effectiveness of 4 treatment regimens: gemcitabine alone, gemcitabine plus conventional radiotherapy, gemcitabine plus intensity-modulated radiotherapy (IMRT); and gemcitabine with stereotactic body radiotherapy (SBRT). Patients transitioned between the following 5 health states: stable disease, local progression, distant failure, local and distant failure, and death. Health utility tolls were assessed for radiotherapy and chemotherapy treatments and for radiation toxicity. SBRT increased life expectancy by 0.20 quality-adjusted life years (QALY) at an increased cost of USD 13,700 compared with gemcitabine alone (incremental cost-effectiveness ratio [ICER] = USD 69,500 per QALY). SBRT was more effective and less costly than conventional radiotherapy and IMRT. An analysis that excluded SBRT demonstrated that conventional radiotherapy had an ICER of USD 126,800 per QALY compared with gemcitabine alone, and IMRT had an ICER of USD 1,584,100 per QALY compared with conventional radiotherapy. A probabilistic sensitivity analysis demonstrated that the probability of cost-effectiveness at a willingness to pay of USD 50,000 per QALY was 78 percent for gemcitabine alone, 21 percent for SBRT, 1 percent for conventional radiotherapy, and 0.01 percent for IMRT. At a willingness to pay of USD 200,000 per QALY, the probability of cost-effectiveness was 73 percent for SBRT, 20 percent for conventional radiotherapy, 7 percent for gemcitabine alone, and 1 percent for IMRT. The current results indicated that IMRT in locally advanced pancreatic cancer exceeds what society considers cost-effective. In contrast, combining gemcitabine with SBRT increased clinical effectiveness beyond that of gemcitabine alone at a cost potentially acceptable by today's standards [463].

Other non-surgical, non-pharmacological treatment of pancreatic cancer

Cryoabladation

To examine whether thermo-perfusion of the bile duct and duodenum may protect these organs during cryoablation of adjacent pancreatic tissue cryoablation of the pancreatic tissue, adjacent to the common bile duct and duodenum was performed in two groups of pigs. In the experimental group, the bile duct and duodenum were protected during the cryo-procedure by intraluminal perfusion of warm saline. In the control group, cryoablation was performed without thermo-protection. All three animals in the control group developed duodenal perforation and abscesses and died within a week. All the pigs in the experimental group survived and on re-operation 14 days after the first procedure were found to have normal duodenum and bile duct adjacent to the cryoablated pancreatic tissue. Histological

examinations confirmed these results. The present study confirms the feasibility and efficacy of thermo-protection of the duodenum and common bile duct during cryoablation of the head of the pancreas [464].

Pancreatic cancer is the fourth leading cause of cancer-related death. Cryosurgery has emerged as a promising new technique for treatment. Although 80 percent of pancreatic cancers are located in the pancreatic head, no research has been conducted on the safety and efficacy of cryosurgery for these tumors. Two groups of Tibetan miniature pigs (n=4 per group) underwent cryosurgery to the pancreatic head with either the deep freezing protocol (100 % argon output) or shallow freezing protocol (10 % argon output), and compared to sham-operated pigs. Serum inflammatory factors and amylase increased during the 5 days after cryoablation in both groups but acute pancreatitis did not occur. Adhesions were observed between the pancreatic head and adjacent organs, and only minor trauma was caused to the stomach, duodenum, small intestine, and liver. Ice balls with a radius of 0.5 cm beyond the tumor edge were sufficient to cause complete necrosis of the pancreatic tissue, and decreased the degree of cold injury to surrounding tissues. Therefore, shallow freezing protocol seemed to be safer than, and just as effective as, the deep freezing protocol. This preliminary study suggests that cryosurgery could potentially be an effective treatment of cancer of the pancreatic head [465].

Irreversible electroporation therapy

Locally advanced pancreatic cancer patients have limited options for disease control. Local ablation technologies based on thermal damage have been used but are associated with major complications in this region of the pancreas. Irreversible electroporation (IRE) is a nonthermal ablation technology that has been shown is safe near vital vascular and ductal structures. The aim of this study was to evaluate the safety and efficacy of IRE as a therapy in the treatment of locally advanced pancreatic cancer. It was performed a prospective multiinstitutional pilot evaluation of patients undergoing IRE for locally advanced pancreatic cancer from 2009 to 2011. These patients were evaluated for 90-day morbidity, mortality, and local disease control. Twenty-seven patients (13 women and 14 men) underwent IRE, with median age of 61 years (range 45 to 80 years). Eight patients underwent margin accentuation with IRE in combination with left-sided resection (n=4) or pancreatic head resection (n=4). Nineteen patients had in situ IRE. All patients underwent successful IRE, with intraoperative imaging confirming effective delivery of therapy. All 27 patients demonstrated nonclinically relevant elevation of their amylase and lipase, which peaked at 48 hours and returned to normal at 72 hour postprocedure. There has been one 90-day mortality. No patient has shown evidence of clinical pancreatitis or fistula formation. After all patients have completed 90-day follow-up, there has been 100 percent ablation success. IRE ablation of locally advanced pancreatic cancer tumors is a safe and feasible primary local treatment in unresectable, locally advanced disease. Confirming these early results must occur in a planned phase II investigational device exemption (IDE) study to be initiated in 2012 [466].

Experimental

MRI

One study aimed to study magnetic resonance imaging (MRI) findings of pancreatic ductal adenocarcinomas (PDAs) induced by N-nitrosobis (2-oxopropyl) amine (BOP) in Syrian hamsters. A total of 101 female hamsters, 8 weeks old, were randomized into 3 groups. They were randomized into a BOP-treated group (n=80; with weekly subcutaneous injections of BOP, 10 mg/kg body weight, for 7 consecutive weeks), a saline-treated group (n=16), and an

untreated group (n=5). Hamsters underwent abdominal MRI on 1.5-T MR scanners with a dedicated animal radiofrequency coil. Findings of the tumor from the MRI were compared those from histology. Pancreata in the saline-treated and in the untreated groups were normal. In the BOP-treated group, there were 23 and 31 BOP-induced PDAs on macroscopy and microscopy, respectively. Of the PDAs detected on macroscopy, 65 percent were depicted on MRI. As early as 13 and 19 weeks after the first injection of BOP, PDAs in hamsters were found on histology and MRI, respectively. Moreover, the tumor volume on MRI was correlated with the tumor weights excised (n=15). N-nitrosobis (2-oxopropyl) amine successfully induced PDAs in hamsters. Magnetic resonance imaging has the ability to detect healthy pancreas and PDAs in hamsters and has the potential to monitor the development of PDAs [467].

Stromal inflammatory cells

The histologic presence of macrophages (tumor-associated macrophages-TAMs) and neutrophils (tumor associated neutrophils-TANs) has been linked to poor clinical outcomes for solid tumors. The exact mechanism for this association with worsened prognosis is unclear. It has been theorized that TAMs are immunomodulated to an alternatively activated state and promote tumor progression. Similarly, TANs have been shown to promote angiogenesis and tumor detachment. TAMs and TANs were characterized for activation state and production of prometastatic mediators in an immunocompetent murine model of pancreatic adenocarcinoma. Specimens from liver metastases were evaluated by immunofluorescence and immunoblotting. TAMS have upregulated expression of CD206 and CD163-markers of alternative activation but do not have increased expression of classically activated macrophage markers CCR2 and CCR5. TAMs also express Oncostatin M (OSM). It was found TANs, not TAMs, predominately produce MMP-9 in this metastatic tumor microenvironment, while MMP-2 production is pan-tumoral. Moreover, increased expression of VEGF co-localized with TAMs as opposed to TANs. TAMs and TANs may act as distinct effector cells, with TAMs phenotypically exhibiting alternative activation and releasing OSM and VEGF. TANs are localized at the invasive front of the metastasis where they co-localized with MMP-9. Improved understanding of these interactions may lead to targeted therapies for pancreas adenocarcinoma [468].

Surviving pancreatic cancer cells after exposure to gemcitabine or 5-fluorouracil

One of the hallmarks of pancreatic cancer is its inherent insensitivity to chemotherapy. One study was undertaken to develop a cell model for the study of de novo resistance of pancreatic cancer. The surviving pancreatic cancer cells after a 3-day exposure to gemcitabine or 5-fluorouracil followed by another 7-day recovery were potentially drug-resistant. They had similar morphology and comparable growth and tumorigenic potentials to their untreated parental cells. Repeated subculture affected the cell-cycle profile and growth characteristics of the surviving cells. The data suggest that surviving pancreatic cancer cells after drug treatment are a useful model for exploring intrinsic resistance [469].

Zoledronic acid

In one study, it was examined the cytotoxic effects of combination therapy with zoledronic acid (ZOL) and gemcitabine (GEM) on pancreatic cancer cells in vitro and in vivo. Four human pancreatic cancer cell lines were treated with ZOL, GEM or a combination of both, and the effects of the respective drug regimens on cell proliferation, invasion and matrix metalloproteinase (MMP) expression were examined. A pancreatic cancer cell line was also intrasplenically or orthotopically implanted into athymic mice and the effects of these drugs on tumor metastasis and growth in vivo were evaluated by histological and immunohistochemical analyses. Combination treatment with low doses of ZOL and GEM efficiently

inhibited the proliferation and invasion of pancreatic cancer cells in vitro. Western blotting assay revealed that MMP-2 and MMP-9 expression levels were decreased after ZOL treatment. In vivo, combined treatment significantly inhibited tumor growth and the development of liver metastasis. These data revealed that ZOL and GEM, when used in combination, have significant antitumor, anti-metastatic and anti-angiogenic effects on pancreatic cancer cells. The present study is the first to report the significance of the combination treatment of ZOL and GEM in pancreatic cancer using an in vivo model. These data are promising for the future application of this drug regimen in patients with pancreatic cancer [470].

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Overview

Intraductal papillary mucinous neoplasm (IPMN) is a grossly visible (≥1 cm), mucin-producing neoplasm that arises in the main pancreatic duct and/or its branches. Patients with intraductal papillary mucinous neoplasm can present with symptoms caused by obstruction of the pancreatic duct system, or they can be asymptomatic. There are 3 clinical subtypes of intraductal papillary mucinous neoplasm: main duct, branch duct, and mixed. Five histologic types of intraductal papillary mucinous neoplasm are recognized: gastric foveolar type, intestinal type, pancreatobiliary type, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm. Noninvasive intraductal papillary mucinous neoplasms are classified into 3 grades based on the degree of cytoarchitectural atypia: low-, intermediate-, and high-grade dysplasia. The most important prognosticator, however, is the presence or absence of an associated invasive carcinoma. Some main duct-intraductal papillary mucinous neoplasms progress into invasive carcinoma, mainly tubular adenocarcinoma (conventional pancreatic ductal adenocarcinoma) and colloid carcinoma. Branch duct-intraductal papillary mucinous neoplasms have a low risk for malignant transformation. Preoperative prediction of the malignant potential of an intraductal papillary mucinous neoplasm is of growing importance because pancreatic surgery has its complications, and many small intraductal papillary mucinous neoplasms, especially branch duct-intraductal papillary mucinous neoplasms, have an extremely low risk of progressing to an invasive cancer. Although most clinical decision making relies on imaging, a better understanding of the molecular genetics of intraductal papillary mucinous neoplasm could help identify molecular markers of high-risk lesions. When surgery is performed, intraoperative frozen section assessment of the pancreatic resection margin can guide the extent of resection. Intraductal papillary mucinous neoplasms are often multifocal, and surgically resected patients should be followed for metachronous disease [471].

Natural history

The process of Intraductal papillary mucinous neoplasms (IPMN) follows the adenoma-tocarcinoma sequence. If it progresses to malignancy about 5 years is required. Even though the process is slow IPMN provides the clinician with the opportunity to avoid malignancy if the patient is at risk. The natural history as observed through Kaplan Meier event curves for occurrence of malignancy show the process to malignancy is much faster (50 % within 2 years) if pancreatitis-like symptoms are present or if the main pancreatic duct (MPD) is involved. Almost all decisions to resect (95 % in our experience) are based on the presence of symptoms or the MPD location. Cyst size is used infrequently. Every patient with an IPMN should always have a planned follow-up and the frequency depends on the perceived risk of malignancy-immediate imaging if becomes symptomatic to every 2 to 3 years if asymptomatic side branch lesions. The natural history provides modern guidelines for making decisions in patients with a newly discovered IPMN [472].

Proteomics of mucous

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas evolve from dysplasia to invasive adenocarcinoma. The aims of one study were to look for candidate protein profiles in IPMN mucus according to histological grade, using a differential proteomic technique, and to highlight protein peaks associated with malignant transformation. Forty-three mucus samples obtained from surgically resected IPMN and categorized as benign (low/moderate dysplasia) or malignant (severe dysplasia/invasive adenocarcinoma) in 21 and 22 patients,

respectively. A surface-enhanced laser desorption ionization time-of-flight mass spectrometry was used to determine candidate protein expression profiles. Protein peaks that significantly differed between benign/malignant IPMN (area under curve > 0.88; high intensity) were identified using adapted software. Among 952 protein peaks, 31 were differentially expressed in benign/malignant IPMN. Among them, 5 candidate proteins of interest (mass-to-charge ratio [m/z]: 5217, 6326, 6719, 10,453, and 10,849 d) were selected by their high diagnostic accuracy and ability to distinguish between malignant and benign tumors. No correlation was found between peak profiles and duct involvement. It was concluded that carcinogenic process in IPMN is associated with changes in mucus proteome with characteristic peaks that could be potential candidate biomarkers of malignancy [473].

Histopathology

Intraductal papillary mucinous neoplasms (IPMN) are precursor lesions of ductal adenocarcinoma of the pancreas and one of the most common cystic entities in this organ. Branch and main duct types are further distinguished based on the tumor localization. An additional classification is based on the predominant architecture and immunohistochemical profile with four prognostic relevant subtypes, gastric, intestinal, pancreato-biliary and oncocytic. This review provides an overview about the malignant potential of the different subtypes and the prognosis of associated invasive tumors and gives recommendations for the pathological assessment of resection specimens with IPMNs [474].

Multifocality

Intraductal papillary mucinous neoplasms (IPMNs) are a heterogeneous group of mucin producing cystic tumors that involve the main pancreatic duct and/or branch ducts and may be associated with invasive carcinoma. Predicting the risk of malignant transformation of an IPMN lesion can be challenging. The Sendai criteria, based in large part on radiographic imaging features, help guide surgical intervention based on the stratification of cysts into high and low risk lesions for malignancy. Invasive carcinoma may develop in the index IPMN lesion or in a separate site within the pancreas, supporting the concept of a field defect in IPMN tumorigenesis. This stresses the importance of evaluation of the entire pancreas upon diagnosis of IPMN and continued surveillance of the residual pancreas following resection [475].

Intraductal papillary mucinous neoplasms are increasingly diagnosed cystic precursor lesions of pancreatic cancer. Intraductal papillary mucinous neoplasms can be multifocal and a potential cause of recurrence after partial pancreatectomy. To examine the clinicopathologic features and clonal relationship of multifocal intraductal papillary mucinous neoplasms (IPMNs) of the pancreas 34 patients with histologically documented multifocal IPMNs were collected and their clinicopathologic features catalogued. In addition, thirty multifocal IPMNs arising in 13 patients from 3 hospitals were subjected to laser microdissection followed by KRAS pyrosequencing and loss of heterozygosity (LOH) analysis on chromosomes 6g and 17p. Finally, it was sought to assess the clonal relationships among multifocal IPMNs. It was identified 34 patients with histologically documented multifocal IPMNs. Synchronous IPMNs were present in 29 patients (85 %), whereas 5 (15 %) developed clinically significant metachronous IPMNs. Six patients (18 %) had a history of familial pancreatic cancer. A majority of multifocal IPMNs (86 % synchronous, 100 % metachronous) were composed of branch duct lesions, and typically demonstrated a gastric-foveolar subtype epithelium with low or intermediate grades of dysplasia. Three synchronous IPMNs (10 %) had an associated invasive cancer. Molecular analysis of multiple IPMNs from 13 patients demonstrated nonoverlapping KRAS gene mutations in 8 patients (62 %) and discordant LOH profiles in 7 patients (54 %); independent genetic alterations were established in 9 of

the 13 patients (69 %). It was concluded that the majority of multifocal IPMNs arise independently and exhibit a gastric-foveolar subtype, with low to intermediate dysplasia. These findings underscore the importance of life-long follow-up after resection for an IPMN [476].

Subtypes

Intraductal papillary mucinous neoplasm (IPMN) is recognized as a precursor lesion to pancreatic cancer, a unique pathological entity. IPMN has subtypes with different clinical characteristics. However, the molecular mechanisms of cancer progression from IPMN remain largely unknown. In one study it was examined the differences in genetic alteration(s) among the IPMN subtypes. Surgically resected IPMNs (n=25) were classified into four subtypes by hematoxylin and eosin (H&E) and mucin immunostaining. Mutations in KRAS, BRAF, and PIK3CA genes and expression of CDKN2A, TP53, SMAD4, phospho-ERK, and phospho-SMAD1/5/8 proteins were examined. There were 11 gastric, 11 intestinal, one pancreatobiliary, and two oncocytic types in this study. We then compared the two major subtypes, gastric-type and intestinal-type IPMN. Gastric-type IPMN showed a significantly higher incidence of KRAS mutations (9/11, 82 %) compared with intestinal type (3/11, 27 %), although the intestinal type showed a higher grade of dysplasia than gastric type (p < 0.01). All cases with KRAS mutations showed phospho-ERK immunostaining. In contrast, intestinal type (9/11, 81.8%) showed more frequent SMAD1/5/8 phosphorylation compared with gastric-type IPMN (3/11, 27 %). There may be distinct mechanisms of pancreatic cancer progression in the different subtypes of IPMN. In particular, KRAS mutation and bone morphogenetic protein-SMAD signaling status may be crucial diverging steps for the two representative pathways to pancreatic cancer in IPMN patients [477].

Imaging

The intraductal papillary mucinous neoplasm (IPMN) is the most frequent cystic neoplasm of the pancreas. The most important diagnostic technique is contrast-enhanced multidetector computed tomography (MDCT), which most frequently allows the differentiation from other cystic lesions and enables the attribution to branch duct or main duct IPMN. Magnetic resonance imaging (MRI) in combination with magnetic resonance cholangiopancreato-graphy (MRCP) and endoscopic ultrasound are superior in depicting the fine architecture of cystic tumors. Particularly for evaluation of malignant transformation and extent of malignant disease, high resolution imaging is essential. Whereas main duct IPMN is an indication for resection therapy for small and asymptomatic branch duct IPMN periodic surveillance at 6-12 month intervals is recommended [478].

EUS

The preoperative diagnosis of branch duct intraductal papillary mucinous neoplasm (IPMN) of the pancreas can be very difficult, since low-risk and high-risk lesions can be difficult to differentiate even after cytological analysis. The purpose of one study was to evaluate the preoperative diagnostic value of endoscopic ultrasonography (EUS) in differentiating low-risk and high-risk IPMNs. It was retrospectively identified 36 patients who underwent preoperative EUS for branch duct IPMNs. The pathological diagnosis after surgical resection was low-grade dysplasia (n=26), moderate dysplasia (n=1), high-grade dysplasia or carcinoma in situ (n=5), and invasive carcinoma (n=4). It was divided the patients into two groups: low risk (low-grade dysplasia or moderate dysplasia) and high risk (high-grade dysplasia or carcinoma). We focused on the diameter of the cystic dilated branch duct, the main pancreatic duct, and the mural nodule as measured using the EUS findings. The cystic dilated branch duct diameter (32 mm vs 42 mm) was significantly correlated with low-risk and

high-risk IPMNs, but the main pancreatic duct diameter (5.4 mm vs 5.4 mm) was not significantly correlated with the low-risk and high-risk IPMNs. The mural nodule diameter of the papillary protrusions (4 mm vs 16 mm) and the width diameter of the mural nodule (6 mm vs 23 mm) were significantly correlated with low-risk and high-risk IPMNs. It was concluded that the mural nodule of papillary protrusions diameter and width diameter observed using EUS was a reliable preoperative diagnostic finding capable of distinguishing low-risk and high-risk IPMNs [479].

MRI

To evaluate the differentiating factors for intraductal papillary mucinous neoplasm of the pancreas and chronic pancreatitis as determined by MR imaging, during a three-year period, it was performed MR imaging on 33, consecutive patients with IPMN and on 41 patients with chronic pancreatitis. All IPMNs were confirmed by surgery. Two radiologists retrospectively analyzed the ductal change, the cyst shape, CBD dilatation, lymphadenopathy, and parenchymal change. The sensitivity and specificity were calculated for each MRI findings using the Chi square test. Statistically significant MR findings were further analyzed using multivariate logistic regression analysis. The diagnostic performance was evaluated according to the area under the receiver operating characteristic curve (A_z) using specific MRI findings. Statistically specific findings for IPMN compared with those for chronic pancreatitis, were duct dilatation without stricture (specificity 95 %, sensitivity 76 %), bulging ampulla (specificity 98 %, sensitivity 30 %), nodule in a duct (specificity 100 %, sensitivity 15 %), grape-like cyst shape (specificity 98 %, sensitivity 79 %), and nodule in a cyst (specificity 100 %, sensitivity 24 %). Statistically specific findings for chronic pancreatitis compared with those for IPMN, were duct dilatation with strictures (specificity 94 %, sensitivity 95 %), the presence of a stone (specificity 97 %, sensitivity 56 %), and a unilocular cyst shape (specificity 94 %, sensitivity 34 %). Duct dilatation without stricture and a grape-like cyst shape were independently associated with the IPMN. Duct dilatation with strictures was independently associated with the chronic pancreatitis. Interobserver agreement was good to excellent for each finding. Highly specific findings for IPMN include duct dilatation without stricture, bulging ampulla, nodule in a duct, grape-like cyst shape, and nodule in a cyst. MRI is very useful for differentiating IPMN from chronic pancreatitis using these specific findings [480].

Differential diagnosing

On abdominal CT scans asymptomatic cystic lesions of the pancreas are accidentally detected in 1-2 percent of patients. Congenital cysts and pancreatic pseudocysts account for two thirds of these lesions. Pancreatic pseudocysts are a frequent complication of acute and chronic pancreatitis. Among resected cystic neoplasms serous cystic adenoma accounts for 30 percent, mucinous cystic neoplasms for 45% and intraductal papillary mucinous neoplasms for 25 percent. The diagnosis of a cystic pancreatic lesion is usually made by diagnostic imaging. Symptomatic lesions require definitive therapeutic treatment after appropriate diagnostic work-up. In the diagnosis of asymptomatic cystic lesions several factors are important, among them whether the cyst is connected to the pancreatic duct (as in IPMN and pseudocysts), the size of lesion (for treatment indications) and whether nodules form in the wall of the cyst (a sign of potential malignancy). EUS-guided fine needle aspiration of the cyst fluid adds to the discrimination between benign, premalignant and malignant cystic lesions. Measuring lipase activity, CEA, viscosity and mucin as well as cytology can help in differentiating cystic lesions. An algorithm is discussed for the differential diagnosis and for selection of the appropriate treatment for pancreatic cystic lesions, most of which never require surgery [481].

Immunobiology

Having the characteristic features of elevated serum IgG4 levels and prominent infiltration of IgG4-positive plasma cells with fibrosis in lesions, Mikulicz's disease (MD) has been recognized as an IgG4-related disease (IgG4-RD). Although incidence of autoimmune pancreatitis (AIP), one of the organ characteristics of IgG4-RD, has been internationally reported, there are only a few such reports of IgG4-related MD. The limited number of reports might be attributable to the low recognition of IgG4-related MD as a clinical entity as well as its misdiagnosis as Sjögren's syndrome (SS). Thus, we compared several clinical features of MD with SS to improve proper clinical diagnosis of MD in the clinical setting. A total of 70 SS and 70 MD cases evaluated in Japan were retrospectively analyzed. In SS patients, sicca symptoms were the most frequent (87 %), followed by articular symptoms (23 %), while lacrimal and salivary gland swelling were a rare (10 %) and transient manifestation. In contrast, lacrimal or salivary gland swelling was observed in all patients with MD. Although nearly 60% of MD patients complained of sicca syndrome, skin rash and arthralgia were rare symptoms. Hypergammaglobulinemia was recognized in both SS and MD patients, but the occurrence of autoantibodies in patients with IgG4-related MD was low. Extraglandular organ involvement, often involving the retroperitoneum, pancreas, kidney and lung, was often discovered at the time of IgG4-related MD diagnosis. Although corticosteroid therapy tended to delay the hypofunction of salivary gland in SS patients, recovery of decreased function of salivary glands were observed in IgG4-related MD patients. These results suggest the beneficial effect of aggressive corticosteroid intervention in patients with IgG4-related MD. Although SS and MD are both chronic inflammatory diseases affecting the lacrimal and salivary glands, their clinical features and corticosteroid responsiveness are different. Thus, differential diagnosis of these conditions is warranted [482].

Familary and hereditary IPMNs

The prevalence of intraductal papillary mucinous neoplasms in patients with a high risk of pancreatic adenocarcinoma was estimated to be 15 percent. However, a familial form of intraductal papillary mucinous neoplasms was never described. Three families (8 patients) with intraductal papillary mucinous neoplasms familial forms were described. Diagnosis was made according to radiological criteria and was confirmed by pathological data. Genetic predisposing factors of pancreatic cancer were searched for. Symptoms related to intraductal papillary mucinous neoplasms were recurrent acute pancreatitis (n=3) or fortuitous discovery (n=5). Number of cystic lesions was ≤ 3 (n=4) or ≥ 3 (n=4). Intraductal papillary mucinous neoplasms involved branch ducts (n=7) or both main pancreatic duct and branch duct (n=1). Severe and moderate dysplasia was found on surgical specimens. No genetic alteration was found (BRCA2, p16 or CDKN2A genes). A familial form of intraductal papillary mucinous neoplasms was found in three families. No pancreatic cancer was found in relatives but an attentive survey has to be proposed [483].

Intraductal papillary mucinous neoplasm (IPMN) is a rare pancreatic tumor defined as intraductal mucin-producting neoplasm with tall, columnar, mucin-containing epithelium. IPMN have already been described in association with inherited genetic disorder including familial adenomatous polyposis and Peutz-Jeghers syndrome. However, there is no reported description of familial history of IPMN. It was reported in a case-report IPMN in the first-degree relatives without familial history of colorectal polyposis or previous extra-pancreatic cancer. The rarety of IPMN suggests that the coexistence of this tumor in two first-degree relatives is probably due to a genetic inherited factor that remains to be elucidated [484].

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Labelling index

Intraductal papillary mucinous neoplasms (IPMNs) are pathologically classified as IPMN with low- or intermediate-grade dysplasia, IPMN with high-grade dysplasia, and IPMN with an associated invasive carcinoma. A stepwise carcinogenic pathway has been considered for IPMN. However, it is not obvious when surgical resection should be performed for IPMN. It was studied the MIB-1 labeling index in cases of IPMN and ordinary ductal adenocarcinoma (ODA). Moreover, IPMN with an associated invasive carcinoma was divided into 2, namely, carcinoma in situ and invasive components, and the respective MIB-1 labeling indexes were examined. The MIB-1 labeling index for IPMN with low- or intermediate-grade dysplasia (2 %) was significantly lower than those for IPMN with high-grade dysplasia (14 %), both the carcinoma in situ components (23 %) and invasive components (19 %) within the IPMN with an associated invasive carcinoma, and ODA (20 %). The 5-year survival rates after resection were 100% for IPMN with low- or intermediate-grade dysplasia, 83 percent for IPMN with high-grade dysplasia, 54 percent for IPMN with an associated invasive carcinoma, and 10 percent for ODA. It was concluded that MIB-1 might be useful for the classification of malignant potential in IPMN. Intraductal papillary mucinous neoplasm should be surgically resected when the tumor is diagnosed as IPMN with high-grade dysplasia [486].

Slow growth

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a relatively rare clinical entity with a main characteristic being mucus production. Extension of IPMN along pancretic ducts and mucus production lead to ductal obstruction and dilatation, resulting in recurrent episodes of acute pancreatitis. The molecular background of IPMN comprises several aberrations, with the K-ras gene mutation being the likely trigger that initiates further genetic changes. Due to its indolent nature, IPMN is most commonly diagnosed in the 7th decade of life. Depending on the histology type, IPMN has a malignant potential. Therefore, surgical therapy remains a "gold standard" of treatment. Insidious, slow progression of the disease and absence of symptoms in a certain number of patients makes diagnostic approach to this entity difficult. In one paper it was presented a patient with IPMN of the pancreas, in whom the episodes of acute pancreatitis had been present for 22 years [487].

Branch duct type intraductal papillary mucinous neoplasm

Main duct type IPMN has been recommended for resection. However, the indications for resection of the branch duct type IPMN have been controversial. It was retrospectively analyzed the clinicopathological factors of 134 patients undergoing resection for branch duct type IPMN, excluding main duct type IPMN, to identify predictors of the malignant behavior of this neoplasm. The cutoff values of tumor size, main pancreatic duct (MPD) size, mural nodule size, and carcinoembryonic antigen (CEA) level in the pancreatic juice obtained during preoperative endoscopic retrograde pancreatography (ERP) were analyzed using receiver-operator characteristic curves. It was found 7 significant predictors for malignancy in the branch duct type IPMN in a univariate analysis; jaundice, tumor occupying the pancreatic

head, MPD size >5 mm, mural nodule size >5 mm, serum carbohydrate antigen (CA)19-9 level, positive cytology in the pancreatic juice, and CEA level in the pancreatic juice >30 ng/mL. In a multivariate analysis, a mural nodule size >5 mm and a CEA level in the pancreatic juice >30 ng/mL were independent factors associated with malignancy. The positive predictive value of a mural nodule size >5 mm and a CEA level in the pancreatic juice >30 ng/mL was 100 percent, and the negative predictive value was 96 percent. It was identified 2 useful predictive factors for malignancy in branch duct type IPMN; a mural nodule size >5 mm and a CEA level in the pancreatic juice >5 mm and a CEA level in the pancreatic juice obtained by preoperative ERP >30 ng/mL [488].

It has been reported that main duct intraductal papillary mucinous neoplasms are more invasive and have a worse prognosis than branch duct intraductal papillary mucinous neoplasms. Therefore, an aggressive surgical approach has mainly been recommended for all MD-IPMNs. However, the surgical management of BD-IPMNs has been controversial and the consensus guidelines are not specific for an indicator of malignancy in BD-IPMNs. The objective of this study was to determine the proper management and follow-up strategy of BD-IPMNs. It was monitored and analysed patients with presumed BD-IPMNs between 1995 and 2010. The mean value of the initial cyst size in all patients with BD-IPMNs was 2.2 cm. Amongst 194 patients with BD-IPMNs, 34 underwent immediate surgical resection, 152 were followed conservatively. Amongst the 152 conservatively managed patients, 18 (12 %) underwent surgical resection after a median follow-up of 12.7 months (range, 3-48 months). In 132 patients who were managed conservatively without surgery, the mean incremental rate of cvst size growth was 0.0038 cm/month during a median of 31 months of follow-up and there were no IPMN-related deaths. It was concluded that amongst patients with BD-IPMNs, about 10 percent have surgery within approximately 1 year from the time of diagnosis because of the occurrence of new malignant stigmata. Therefore, a conservative approach without surgery and careful follow-up every 3 months or 6 months during the first year after diagnosis can be safely advocated in patients with BD-IPMNs larger than 10mm in size who have no risk factors for malignant IPMNs [489].

The aim of one study was to perform a 10-year imaging and clinical prospective follow-up of patients with nonoperated branch duct (BD) intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. Forty-nine patients with BD-IPMN who displayed a low probability for malignancy were followed up including a clinical component and a series of imaging techniques such as computed tomography, magnetic resonance cholangiopancreatography, and endoscopic ultrasonography. After a mean follow-up period of 77 months, 78 percent of patients remained free of symptoms. An increase in the size and number of BD cysts without mural nodules and with no significant increase of main duct size occurred in 18 patients at an average interval of 47 months. Five patients were operated on owing to recurrent pancreatitis and/or an increase in the size of either cysts or the main duct (mean time delay after diagnosis: 20 months). Pathologically, they were diagnosed as benign adenoma (n=1) or borderline (n=4). It was concluded that the long-term clinical and imaging follow-up indicated that none of the patients with BD-IPMNs developed malignancy. Therefore, BD-IPMNs with no signs of malignancy should be managed conservatively. It was propose that following a 2-year patient follow-up, biannual imaging follow-ups could be sufficient [490].

In patients with branch duct intraductal papillary mucinous neoplasms of the pancreas (BD-IPMN), the risk of malignant progression is well described at short- and mid-term. Few data beyond 5 years are available. It was performed a prospective study in consecutive patients with BD-IPMN and follow-up (F/U) \geq 60 months to assess long term risk of malignant progression. All computed tomographies and magnetic resonance cholangiopancreato-graphies performed every 1 or 2 years (depending on the maximum size of cyst) were read by the same radiologist. EUS was performed in case of occurrence of main pancreatic duct (MPD) dilation or mural nodule >5 mm. Size increase was considered significant if >5 mm. Size variation, criteria suggestive of malignancy, operative therapy and pathology were

recorded. Fifty-three patients were included (median age at diagnosis: 61 years, median F/U: 84 months (range: 60-132) including 5 F/U >120 months). Lesions were stable in 38 patients (72 %). Size increased in 8 patients (15 %) (median increase: 11 (5-33) mm) without mural nodule (MN). One of those was operated on (low-grade dysplasia). A MN appeared in 5 patients (9 %). More than 5 mm nodules were seen in 2 patients (5 and 15 mm) who were operated on (intermediate-grade dysplasia in both). The 3 remaining pts (MN < 5 mm) were carefully followed-up. Invasive advanced carcinoma occurred in 2 patients, both after 84 months F/U. In one of these, no imaging changes were noted 12 months before diagnosis of malignancy. It was concluded that in BD-IPMN, the risk of malignant evolution persists after 60 months F/U including invasive carcinomas. F/U imaging surveillance is still necessary beyond this delay in patients fit for potential surgery [491].

Evaluation with MDCT

The purpose of one study was to evaluate factors predictive of the malignant grade associated with branch duct type intraductal papillary mucinous neoplasm (BD-IPMN) using multidetectorrow computed tomography (MDCT). It was reviewed the morphological features of 26 BDIPMNs using MDCT. Tumor size, caliber of the main pancreatic duct, number of mural nodules, diameter of the largest mural nodule and volume of the largest mural nodule were assessed and correlated with the pathological findings. By multiple- and singleregression analyses and Mann-Whitney U test, significant differences in the caliber of the main pancreatic duct and number of mural nodules were observed between adenoma and non-invasive carcinoma and in the number of mural nodules between adenoma and invasive carcinoma. No significant differences were observed between non-invasive carcinoma and invasive carcinoma. Based on the differential diagnostic criterion of 1 or more mural nodules for distinguishing adenoma from non-invasive carcinoma and invasive carcinoma, the sensitivities were 60 percent and 100 percent, respectively, and the specificity was 93 percent for both. Although it was impossible to distinguish non-invasive carcinoma from invasive carcinoma, MDCT was reliable for distinguishing adenoma from non-invasive carcinoma and invasive carcinoma [492].

Mixed duct type intraductal papillary mucinous neoplasm

The clinical importance of intraductal papillary mucinous neoplasm of the pancreas (IPMN) has been increasing with a large number of newly diagnosed IPMN. This study was designed to explore the characteristics of resected IPMN and to determine the predictive factors for malignant and invasive IPMN. Retrospective review of a prospectively collected database was performed on 187 consecutive patients following IPMN surgery between 1994 and 2008 at a tertiary institute. The main duct type IPMN was radiologically defined as main pancreatic duct dilation >5 mm rather than previously defined ≥10 mm. The morphologic types of IPMN included 28 main duct (IPMN-M, 15 %), 118 branch duct (IPMN-Br, 63 %), and 41 mixed (IPMN-Mixed, 22 %) IPMNs. There were 23 patients with adenoma, 106 borderline atypia, 15 carcinoma in situ, and 43 invasive carcinoma. Sixty-nine extrapancreatic malignancies were diagnosed in 61 (33 %) patients. Based on multivariate analysis, IPMN-M was statistically significant predictor of malignancy/invasiveness. In patients with IPMN-Br, the presence of mural nodule was a predictive factor for malignancy/invasiveness. In patients with IPMN-Mixed, mural nodule and wall thickening (>2 mm) were risk factor for malignanc and invasiveness and elevated CA19-9 for invasiveness. It was concluded that the main pancreatic duct diameter (>5 mm) is a significant predictor for malignancy and invasiveness. Therefore, IPMN patients with main pancreatic duct dilatation (>5 mm) should be considered surgical resection. Mural nodule is the indicator of surgery in IPMN-Br and IPMN-Mixed. In case of IPMN-Mixed with wall thickening or elevated serum CA19-9, surgical resection is recommended [493].

Main duct IPMN

Although surgical resection is recommended for all main duct-type intraductal papillary mucinous neoplasms (IPMNs), controversies remain over the precise surgical strategy that should be adopted. One study thus aimed to investigate the appropriate surgical strategy for main duct IPMNs. It was retrospectively evaluated 46 patients with main duct-type IPMNs who underwent surgical resection at a single center between 1991 and 2010. Results: Only 1 patient underwent total pancreatectomy (TP). Three patients underwent repeated pancreatectomy; TP was performed after distal pancreatectomy (DP) in 2 of these patients and after pylorus-preserving pancreaticoduodenectomy (PPPD) in the remaining patient. The recurrent histology indicated minimally invasive carcinoma in all 3of these patients. Among the 6 patients who died in the study, no deaths occurred due to local recurrence of the remnant pancreas. It was concluded that total pancreatectomy should be considered very selectively in the presence of a malignant lesion spreading to the whole pancreas [494].

Simultaneous intraductal papillary neoplasms of the bile duct and pancreas

Some authors have suggested that intraductal papillary mucinous neoplasms of the bile duct (IPMN-B) could be the the biliary counterpart of IPMN of the pancreas (IPMN-P) since they share several clinical-pathological features. These include prominent intraductal papillary proliferation pattern, a gastrointestinal phenotype, frequent mucin hyper-secretion and progression to mucinous carcinoma. To date there are just four reported cases of patients with synchronous IPMN-B and IPMN-P all of which were treated surgically. It was therefore reported a case of a 76-year-old woman who was incidentally diagnosed with both an asymptomatic 3 cm bulky fluid lesion obstructing the bile duct lumen, diagnosed as a malignant IPMN-B, and synchronous multiple pancreatic cystic lesions (10-13 mm) communicating with an irregular Wirsung, diagnosed as branch duct IPMN-P. Since surgery was ruled-out because of the patient's age and preferences, she underwent a conservative management regimen comprising both chemotherapy and radiotherapy. This was effective in decreasing the mass size and in resolving subsequent jaundice. This is also the first reported case of IPMN-B successfully treated with chemoradiotherapy. Clinicians should consider medical treatment as an option in this clinical scenario, in patients who may be unfit for surgery [495].

Concomitant with pancreatic cancer

IPMN is a slow-growing tumor and has a good prognosis, but is very often associated with a high incidence of pancreatic ductalcarcinoma (DC). Unlike IPMN, DC progresses rapidly, and has a poor prognosis. However, DC concomitant with IPMN has a better prognosis than DC without IPMN. The reason for the good prognosis of the former is undetermined, but perhaps it is the early detection of DC or its not so malignant behavior. It is important to thoroughly examine the entire pancreas for the potentialco -occurrence of DC in patients with IPMN [496].

Complications to IPMN

Imaging

To correlate the CT and MR images with pathologic findings on intraductal papillary mucinous neoplasms (IPMNs) complicated with intraductal hemorrhage, perforation, and

fistula it was retrospectively evaluated the CT (n=5), MR imaging (n=4), and pathological features of five IPMN patients complicated with intraductal hemorrhage (n=5), perforation (n=1), and fistula into the duodenum and jejunum (n=1). It was concluded that intraductal hemorrhage could be detected as high attenuation on non-contrast CT in two of the five cases, and as high signal intensity on fat-suppressed T1-weighted MR images in all four of the cases. Perforation and fistula could be recognized on CT images. In all IPMNs, denuded epitheliums were observed pathologically. Dissolution of the duct wall and extension of mucinous materials were seen at the area of denuded epithelium. Perforations and fistula, without evidence of cancer invasion, were recognized in the dissolved duct wall. Pathogenesis of the perforations and fistula formations appeared to be related to excessive pressure in the dilated ducts and autodigestion of enzyme-rich fluids. It was concluded that complications with IPMN could be recognized on CT and fat-suppressed T1-weighted MR images. Intraductal hemorrhage might be predictive sign of perforation and fistula formation [497].

Penetrating the stomach

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas occasionally penetrates to others organs. We present a case of IPMN penetrating to the stomach and the common bile duct. A 75-year-old man was admitted to the hospital because of epigastric pain. Computed tomography (CT) showed a papillary tumor protruding into the markedly dilated main pancreatic duct and splenic vein obstruction. The tumor was diagnosed as IPMN arising in the main duct, but he rejected surgery and he was followed without treatment. One year later, gastroduodenoscopy revealed gastropancreatic fistula and we were able to pass an endoscope through the fistula and directly examine the lumen of the main pancreatic duct and the papillary tumor adjacent to the fistula. Absence of malignant cells on histopathology suggested mechanical penetration rather than invasive penetration. CT showed splenic vein reperfusion due to decreased inner pressure of the main pancreatic duct. Two and a half years later, CT revealed biliopancreatic fistula formation. Endoscope biliary drainage was performed but failed. Despite jaundice, he is still ambulatory and seen in the clinic three years after the first admission. It was thus experienced a case of IPMN penetrating to the stomach and the common bile duct that has taken a slow course. It represents the importance of distinguishing mechanical penetration from invasive penetration as well as mechanical splenic vein obstruction from splenic vein invasion [498].

Recurrent acute pancreatitis

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a distinct entity characterized by papillary proliferations of mucin-producing epithelial cells with excessive mucin production and cystic dilatation of the pancreatic ducts. The clinical presentation often involves recurrent episodes of pancreatitis associated with the temporal obstruction of the main pancreatic duct caused by the hypersecretion of mucin. It was described a case in which the patient repeatedly experienced the occurrence of idiopathic acute pancreatitis in the head of the pancreas over a 9-year period, and who was ultimately was cured by distal pancreatectomy for IPMNs in the pancreatic tail. The case illustrates the potential pitfalls in the diagnosis of IPMNs owing to a discrepancy between the site of pancreatitis and that of the IPMN. The possible mechanisms linking acute pancreatitis with the formation of IPMNs are also reviewed [499].

IPMN and aortic aneurysm

Pancreatic surgery concomitant with abdominal aortic repair is rarely chosen due to concerns about prosthetic infection following pancreatic leakage and the poor prognosis of pancreatic

neoplasms. It was reported a successfully treated case of infrarenal abdominal aortic aneurysm and intraductal papillary mucinous neoplasms of the pancreas treated by a one-stage operation. A 75-year-old male with a history of cerebral infarction and chronic subdural hematoma was referred to our department with a pulsatile abdominal mass. A 70-mm infrarenal abdominal aortic aneurysm with severe proximal neck angulation and a 28-mm multilocular cystic tumor with mural nodules in the pancreas body were detected. Abdominal aortic repair with a prosthetic graft and distal pancreatectomy were performed simultaneously. The postoperative course was mostly uneventful, and he was discharged to a rehabilitation facility [500].

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Mucin intraperitoneally

Intraductal papillary mucinous neoplasm (IPMN) is an increasingly recognized pancreatic neoplasm characterized by excessive mucin secretion by ductal epithelial cells resulting in a cystic dilation of the pancreatic duct. The objective of one study was to review one university's experience and the literature to determine the significance of extra-pancreatic mucin when associated with an IPMN. A retrospective analysis at the institution revealed only two cases of IPMN associated with extra-pancreatic mucin, which was classic IPMNs with rupture of the pancreatic duct and peritoneal mucin spillage. This specific finding is not previously described, although is assumed as five cases were reported in the literature with IPMN and mucin extension demonstrated by pseudomyxoma peritonei (PMP). It was proposed IPMN of the pancreas may be grossly compared to a mucocele of the appendix, as both are characterized by excessive secretion of mucin by ductal epithelial cells. A morbid complication of a mucocele is PMP. The presence of extra-pancreatic mucin with an IPMN could present a rare but important marker of the eventual seeding of tumor outside the primary IPMN. This has been documented with cases of iatrogenic spilling of pancreatic mucin, as well as multiple cases of IPMN associated with pseudomyxoma peritonei. At this time, there is scant reporting and consensus for the treatment of IPMN with extra-pancreatic mucin [502].

Enucleation

Accurate indications and the extent of surgery for branch duct intraductal papillary mucinous neoplasm (IPMN) of the pancreas are still debatable. In particular, small tumor is located at the head portion of pancreas presents a dilemma. The purpose of one study is to compare the efficacy of enucleation with that of pancreaticoduodenectomy (PD) in patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreas or uncinate process. Among 155 patients who underwent pancreatic surgery due to pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the head of pancreatic cystic tumors between 2000 and 2007, 14 patients with small (2 cm<size<3 cm) branch duct IPMN located at the hea

underwent PD, and four patients underwent enucleation. It was compared short term surgical outcomes between the two groups. The average age was 62 years and consisted of 8 men and 6 women. The mean operation time and blood loss were significantly lower in EN group. There were no significant differences in other surgical morbidities. The result suggests that enucleation for small branch duct IPMN located at the head of pancreas or uncinate process is feasible and as safe as PD, despite a high rate of minor complications [503].

Prognostic factors

To investigate the clinicopathological features of intraductal papillary mucinous neoplasms and evaluate the prognosis between histopathological groups a retrospective review of 55 consecutive patients operated between 1991 and 2006, analysis of clinicopathological features and survival was performed. Group I comprised of 9 mild and 14 moderate dysplasias, group II of 11 carcinomas in situ and group III of 21 invasive cancers. Age, diabetes, anorexia and jaundice were significantly more frequent in group III. Thirty-two patients (58 %) presented main duct type which was more frequently associated with invasive carcinoma. Mean tumoral size progress from group I to group III (26 mm vs 27 mm vs 32 mm) as the mean size of the pancreatic duct (6.7 mm vs 7.9 mm vs 11.5 mm). Median follow-up was 154 months with 5-year survival rate of 61 percent. For group I, II and III it was 76, 100, and 26 percent, respectively. Lymph node positivity was associated with poor outcome: 44 percent versus 0 percent (N0 vs N+). It was concluded that the prognosis of non-invasive intraductal papillary mucinous neoplasms of the pancreas is favourable. For patients with invasive cancer, nodal invasion is a factor of worst prognosis [504].

Branch duct IPMN

International consensus guidelines for the management of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas provide several factors that can be used to predict which IPMNs will become malignant. The sensitivity of each factor's predictive accuracy, however, is relatively low, making it difficult to determine the appropriate treatment in individual cases. The aim of one study was to investigate whether increasing the number of predictive factors might augment the sensitivity of the established guidelines to detect malignant IPMNs. The medical records of 138 patients with IPMNs resected at one institution were reviewed. Possible malignant predictors were analyzed by univariate and multivariate analysis, and the effects of the number of factors and the predictive score of the pathologic results were examined. The cutoff points for the number of predictors to discriminate between malignant and nonmalignant IPMNs were established by constructing receiver operating characteristic curves. A predictive analysis could not be carried out for the main duct IPMNs because of the high prevalence of malignancy and the small number of significant predictors associated with them. For malignant branch duct IPMNs, however, we identified 4 predictive factors that helped determine the correct diagnosis as follows:

- the presence of a cyst ≥30 mm in diameter
- the presence of mural nodules
- a history of acute pancreatitis
- atypical results of pancreatic juice cytology

An increase in the number of these factors significantly affected the sensitivity to predict malignancy. The area under the curve for the number of predictors for malignant branch duct IPMNs was 0.86, and the sensitivity and specificity were 96 percent and 71 percent, respectively, when the cutoff point was set at 2. The predictive scoring system also showed the same values of sensitivity and specificity for the number of factors. Patients with branch duct IPMNs who have 2 or more of the 4 predictive factors described above should undergo

standard pancreatectomy with lymph node dissection, whereas patients who present with 0 or 1 predictive factor can be treated by minimal pancreatectomy without nodal dissection or by careful observation without resection. All patients with main duct IPMNs, therefore, should be treated with resection as suspected malignancies [505].

Impact of positive margins and lymph gland involvement

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, defined by the World Health Organization (WHO) in 1996, comprise a histologic spectrum ranging from adenoma with mild dysplasia to invasive carcinoma. Increasing molecular and clinical evidence supports the idea that all IPMNs with invasive carcinoma have progressed from adenomas that underwent transformation, possibly reflecting stepwise molecular genetic changes similar to the adenoma-carcinoma sequence seen in colon cancer. Although the overall outcome for IPMN is good, a significant proportion of patients with resected noninvasive IPMN develops pancreatic adenocarcinoma in the pancreatic remnant and subsequently dies of disseminated disease. It is reported that positive margins (M+) for adenomas and borderline lesions closer to adenomas do not warrant subsequent resection. However, there have been reports of invasive carcinomas in association with only mild or moderate dysplasia (adenomas or borderline lesions) within the IPMN in the remnant pancreas. The management of IPMNs has become increasingly controversial as experience with these tumors has grown, and there is currently no consensus or consistent evidence regarding the value of increased transection margins in reducing recurrence. Furthermore, there is no consensus on whether involvement of LNs represents a risk factor for postoperative margins with adenomas or borderline lesions are therefore controversial, and surgeons thus remain uncertain about how much pancreas to resect, weighing the risk of recurrence against the morbidity of additional resection. Accurate information is currently lacking regarding the values of positive margins (M+) and lymph node (LN) metastases as independent predictors of postoperative recurrence in invasive and noninvasive intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. A comprehensive online literature search identified all types of primary studies that included M+ and LN metastases as risk factors and defined recurrence as an outcome in patients with IPMNs. Suitable articles were also identified by manually researching references in gualifying articles. A meta-analysis of the result was performed using a random effects model. The recurrence rate in noninvasive IPMNs was 4 percent in patients with negative margin (M-) versus 10 percent in those with M+ (odds ratio 0.37, 95 % confidence interval 0.17 to 0.78). The recurrence rate in invasive M- IPMNs in was 34 percent compared to 54 percent in M+ IPMNs (OR 0.47, 95 % confidence interval 0.25 to 0.88). The recurrence rate in invasive IPMNs with positive LN was 77 percent compared to 31 percent with negative LN (OR = 0.15). It was concluded that positive margins were associated with disease recurrence in all patients with IPMN, and nodal metastases were significantly associated with recurrence in invasive IPMN. International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms of the Pancreas indicated that adenoma at the resected margin did not warrant further resection. However, pooled data in the current study indicated that the odds of recurrence of noninvasive IPMNs after resection were significantly associated with M+. Furthermore, available data showed that 54 percent (7/13) of M+ in relapsed noninvasive IPMNs were adenomas (mild dysplasia). Although the data did not prove directly that M+ cause local recurrence, they suggest that M+ is associated with an increased risk of local recurrence. Recurrence of noninvasive tumors has also been reported, even after complete resection. These recurrences may be the results of residual neoplasms, including multifocal disease, which may have been unrecognized at the time of surgery, or of metachronous development of IPMN. Further detailed histological and molecular studies are needed to clarify this issue. Because the chance of recurrence from dysplasia at the resected margin, or from multifocal disease in the remnant pancreas is acceptably low, and some recurrence in the isolated pancreatic remnant can be cured by repeat pancreatectomy it is recommend that the goal of treatment for noninvasive IPMNs should be complete resection with no dysplasia at the

surgical margins, but not prophylactic total pancreatectomy. According to previous reports, LN metastases occurred in 5-54 percent of patients with invasive IPMNs. It was now shown that 52 of 133 patients with invasive IPMNs (39 %) developed LN metastases, which was significantly lower than in those with ductal adenocarcinomas (50-66 %). There is no accurate information regarding the independent predictive value of regional LN involvement for postoperative recurrence in invasive IPMNs; however, the present meta-analysis demonstrated a significant association between LN metastases and recurrence. The incidence of recurrence after resection in LN+ IPMNs was as high as 77 percent, compared to only 31 percent in the LN- group. Previous studies showed that although LN- IPMNs showed improved survival after resection compared with LN- sporadic pancreatic adenocarcinomas, the natural history of LN+ invasive IPMNs mimicked that of LN+ sporadic pancreatic adenocarcinomas. D2 LN dissection might also be applied to IPMNs with mural nodules ≥10 mm in size, or with imaging findings suggestive of possible LN metastasis. Even in the absence of these factors, peripancreatic LN dissection (D1) at least might be advisable in IPMNs with mural nodules, because of the possibility of invasive carcinoma. Extended LN dissection did not benefit overall survival in patients with pancreatic ductal adenocarcinoma. However, no studies have reported on the effectiveness of extended LN dissection for invasive IPMNs, and further studies concerning the effectiveness of extended LN dissection in patients with invasive IPMNs are therefore needed. Chari et al reported that 70 percent of patients with recurrence after complete resection had no nodal metastases or perineural or vascular invasion. This suggests that early extrapancreatic spread through micrometastases may occur in invasive IPMNs, as with pancreatic ductal adenocarcinoma. In conclusion, this meta-analysis demonstrated that the association between margins and the risk of recurrence is largely driven by M+ in all patients with IPMNs, and that LN metastases provide a significant contribution to that risk in invasive IPMNs. It was therefore concluded that segmental resection of noninvasive IPMNs to achieve M- with no dysplasia is likely to have substantial benefits in terms of long-term local control. Extended LN dissection and pancreatectomy might reduce recurrence in the case of invasive carcinomas. However, prophylactic total pancreatectomy should be performed cautiously in both invasive and noninvasive IPMNs [506].

Extrapancreatic malignancies

High rates of extrapancreatic malignancies (EPM) have been observed in patients with intraductal papillary mucinous neoplasm (IPMN). IPMN in patients with familial pancreatic cancer have also been reported. The purpose of one study was to evaluate the association of IPMN with EPM, malignancies in family members, and germline BRCA1 and BRCA2 mutations. Using retrospective analysis on prospectively collected data from 82 patients with IPMN and direct contact for familial cancer history, data were compared with those of 150 patients with pancreatic ductal adenocarcinoma (PDAC). The common germline mutations in the BRCA1 and BRCA2 genes were evaluated on available IPMN patients. EPM rates were greater in IPMN than PDAC patients. Malignancies in first-degree relatives, specifically pancreatic cancer, were more common among IPMN than PDAC patients. IPMN patients with EPM had high rates of relatives with colorectal cancer (31 %). Two of the 51 genetically tested patients (4 %) were BRCA2 mutation carriers, and both had first-degree relatives with pancreatic cancer. One patient fulfilled the Amsterdam criteria for hereditary nonpolyposis colon cancer; however, the neoplasm was microsatellite stable. The results demonstrated high rates of EPM among IPMN patients. There was an increased rate of cancer in families of IPMN patients, specifically pancreatic cancer. A high rate of colorectal cancer in families of IPMN patients who have EPM was also observed. These findings suggest a genetic component in the pathogenesis of IPMN. Possible genetic changes include BRCA2 mutations, which are found in 25 percent of IPMN patients with a family history of pancreatic cancer [507].
Surgery

Pancreatic cystic neoplasms are increasingly recognized, with intraductal papillary mucinous neoplasms of the pancreas (IPMNs) being the most frequently observed type. IPMNs are characterized by mucin production and epithelial growth within the pancreatic ducts, and are generally differentiated according to location: main pancreatic duct, its major side branches, or both (mixed type). IPMNs vary from benign to malignant and are considered precursor lesions of pancreatic adenocarcinoma. However, the exact time to neoplastic transformation and whether all IPMNs progress to malignant tumors is unclear. Surgical resection is warranted for all main-duct and mixed-type IPMNs (they harbor a high risk of malignancy of about 70 %). By contrast, branch-duct IPMNs progress to cancer in only about 30 percent of cases. Thus, according to current guidelines (Sendai criteria), asymptomatic side-branch IPMNs <3 cm in size without suspicious radiological features (such as size progression) can be treated conservatively. Lately, even this approach has become controversial, owing to a number of Sendai-negative IPMNs showing malignant transformation. Although most IPMNs should be resected by standard oncological procedures (including lymphadenectomy), small Sendai-negative IPMNs can be treated with limited resections [508].

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas constitute an increasingly recognized entity of cystic pancreatic tumors which are characterized by mucin production and epithelial growth within the pancreatic ducts and show a wide spectrum of morphologic variants. They may arise in the main pancreatic duct, its major side branches or in both (mixed type). Furthermore, IPMNs are considered as precursor lesions to pancreatic adenocarcinoma. However, it is not clear what the time course of such potential neoplastic transformation might be and whether all lesions progress to malignant tumors. As currently no diagnostic test can reliably differentiate between benign and malignant tumors the majority of newly diagnosed IPMNs should be surgically resected. According to current treatment guidelines (Sendai criteria), only asymptomatic side branch IPMNs of less than 3 cm in diameter without suspicious radiologic features, such as nodules, thickness of the cystic wall or size progression, should be treated conservatively without the need for surgical resection. Recently, this approach has become controversial due to a relevant number of reported Sendai negative IPMNs which revealed malignant transformation on final histological examination. The focus of one review is on the surgical treatment of IPMNs with regard to the current state of knowledge [509].

Pylorus- and spleen-preserving total pancreatoduodenectomy

Total pancreatectomy is recommended for intraductal papillary mucinous tumors with widespread involvement of the entire pancreas. Organ-preserving and minimally invasive surgery should be applied in benign and borderline pancreatic lesions. Pylorus- and spleenpreserving total pancreatoduodenectomy (PpSpTPD) with segmental resection of both splenic vessels was attempted for five patients. The technique was based on the concepts of pylorus-preserving surgical procedures: pancreatoduodenectomy two and distal pancreatectomy with segmental resection of splenic vessels ("extended" Warshaw's procedure). Three patients underwent laparoscopic-assisted PpSpTPD and two underwent open surgery. No mortality was noted. Short-term follow-up (median, 28 months) suggested that all patients tolerated the insulin therapy and showed relatively good nutritional status. Only minimal to moderate perigastric fundal varices were noted without gastrointestinal bleeding. It was concluded that PpSpTPD with segmental resection of both splenic vessels is feasible and safe. Even a minimally invasive approach can be indicated in selected patients [510].

Fate of the pancreatic remnant after resection

To determine the occurrence of new disease in the pancreatic remnant after resection for intraductal papillary mucinous neoplasms a longitudinal level II cohort study was performed. The primary cohort was a "resection cohort" of 203 patients who underwent partial pancreatic resection for an intraductal papillary mucinous neoplasm. The occurrence rate of lesions in the pancreatic remnant after resection for an intraductal papillary mucinous neoplasm, determined by use of an annual computed tomographic scan of the pancreas was recorded. New lesions were observed in the remnant of 17 of the 203 patients (8 %) after a median follow-up of 40 months and a median interval of 38 months from the initial resection. Only 1 of these 17 patients with new lesions had a surgical margin that was positive for an adenoma at the time of resection. Comparing the 17 patients with new lesions with the 186 patients without new lesions, it was found no difference in age, gender, procedure type, location in ductal system, original histology, or original margin status. In the new lesion group, no treatment was used for 12 patients who had side-branch disease detected by imaging (6 % of all patients). Surgical treatment was used for 5 patients (2 % of all patients): 2 with adenomas, 1 with a carcinoma in situ, and 2 with an invasive ductal carcinoma (1 with liver metastases). It was found that, following a partial pancreatic resection for an intraductal papillary mucinous neoplasm and a 40-month follow-up with an annual computed tomographic scan of the pancreas, 17 of 203 patients (8 %) developed a new intraductal papillary mucinous neoplastic lesion in the pancreatic remnant. As follow-up time increases, we suspect that new lesions will constantly appear regardless of whether the surgical margin was negative at initial resection [511].

Recurrence

The detection of intraductal papillary mucinous neoplasms (IPMN) has increased over the last decade, but still, management remains controversial. The main problems are their potential for malignancy and risk of recurrence. The purpose of this study was to determine the predictive factors of recurrence after surgical resection. All patients with IPMN who underwent pancreatectomy with curative intent were considered. Data were collected from a prospective base. From 1994 to 2009, 104 patients underwent pancreatectomy. Twenty-one (20 %) had recurrence, 15 on remnant pancreas (none on pancreatic cut surface) and 6 with distant metastases. Twelve patients had total pancreatectomy (1 awaiting surgery). Thirteen (38 %) of 34 patients with invasive IPMN and 20 (26 %) of 77 with main duct involvement (including combined type) had recurrence. In univariate analysis, American Society of Anesthesiologist score and histological and duct type had a significant impact on recurrence rate. In multivariate analysis, histological type (invasiveness) was the only significant predictive factor for recurrence. The risk of recurrence of IPMN after resection depends on the histological type. According to surgical margin, invasiveness, and the type of duct involved, we identified a high-risk group with invasive main duct lesion and a low-risk group with noninvasive branch duct lesion [512].

Biliary IPMN

Biliary intraductal papillary mucinous neoplasm (B-IPMN) has been proposed as a unique clinicopathologic disease with distinct histopathologic features, although wide acceptance remains controversial. A recent consensus conference classified pancreatic IPMN (P-IPMN) into 4 subtypes (i.e. gastric, intestinal, pancreatobiliary, oncocytic) based on morphologic appearance and mucin (MUC) staining properties. The aim of one study was to determine whether B-IPMN has similar histopathologic and immunologic subtypes to P-IPMN. Specific immunostaining for MUC1, MUC2, and deleted for pancreas cancer, locus 4 were performed

on specimens from 19 patients with a histopathologic diagnosis of B-IPMN. Immunostaining patterns of B-IPMN were correlated with histopathology. Based on histopathology, the following subtypes of B-IPMN were identified: pancreatobiliary n=9 (47 %), intestinal n=8 (42 %), oncocytic n=2 (11 %), and gastric n=0. Pancreatobiliary and oncocytic subtypes of B-IPMN were positive for MUC1 and negative for MUC2, and intestinal subtypes were positive for MUC2 and negative for MUC1. Thirteen of the 19 B-IPMN were associated with invasive carcinoma; loss of deleted for pancreas cancer, locus 4 was found in 6 of 13 invasive components and in 3 of 19 noninvasive components of B-IPMN. Five-year survival for patients with resected B-IPMN and invasive carcinoma was 38 percent, which is similar to that for resected P-IPMN with invasive carcinoma. It was concluded that the histopathologic subtypes and type-specific MUC expression patterns of B-IPMN resemble those of P-IPMN. MUC1 expression and/or absence of MUC2 expression, which correlate with aggressive features of P-IPMN, were found in B-IPMN and correlate with invasive B-IPMN. Loss of deleted for pancreas cancer, locus 4 parallels the findings observed in P-IPMN. These findings provide additional support that B-IPMN is a unique entity with similarities to main duct P-IPMN [513].

Despite an increase in the reports of intraductal papillary neoplasm of the bile duct (IPN-B), the clinical characteristics and long-term prognosis of this disease are not well known compared with those of intraductal papillary mucinous neoplasms of the pancreas. The objective of our study was to compare the clinical features, radiologic findings, and clinical outcomes of IPN-B according to histologic subtype. A retrospective analysis was performed on the medical records of 97 patients diagnosed with IPN-B by pathologic analysis of their surgical specimens between 1995 and 2010. It was compared the clinical manifestations, radiological findings, pathologic grade, curative resection rate, recurrence, and overall survival according to four histologic subtypes: gastric (n=15), intestinal (n=46), pancreaticobiliary (n=33), and oncocytic (n=3), which were classified on the basis of hematoxylin and eosin staining and the immunohistochemical profile of mucin core proteins. Mucin hypersecretion was significantly more frequent in patients with gastric and intestinal types than it was in those with oncocytic and pancreaticobiliary types. There were no significant differences between groups regarding the presence of bile duct stones or tumor location. The frequency of invasive carcinoma in the pancreaticobiliary type was significantly higher than those in the gastric and intestinal types (73 vs 27 and 33 %). When comparing the survival curves according to histologic subtype, patients with pancreaticobiliary type demonstrated significantly worse survival compared to those with gastric and intestinal types. Gastric and intestinal types of IPN-B have similar clinical characteristics compared with the pancreaticobiliary type, which has a worse prognosis [514].

To evaluate multi-detector computed tomography (MDCT) findings of intraductal papillary neoplasm of the bile duct (IPNB), a neoplasm that is considered to be the biliary counterpart of pancreatic intraductal papillary mucinous neoplasm. Two radiologists retrospectively evaluated multiphase contrast-enhanced CT images with 0.5 or 1 mm collimation in 37 consecutive patients with resected IPNB diagnosed by a single pathologist. The CT findings were correlated with the pathological findings concerning invasion of the surrounding organs and vessels. All patients showed bile duct dilatation. An intraductal mass was detected in 36 patients and the following findings were observed: extensive infiltration along the bile duct more than 20mm (n=32), compared with normal hepatic parenchyma, isodense or hyperdense during the late arterial phase (n=31), not hyperdense during the portal-venous and delayed phases (n=36), and intense enhancement rim at the base of the mass during the portal-venous or delayed phase (n=27). Parenchymal invasion of the surrounding organs was seen in eight of 16 tumours showing irregular or bulging margins. Vascular invasion was false positive in four of eight tumours. It was concluded that IPNB exhibits relatively characteristic findings with multiphase contrast-enhanced examination using MDCT. A tendency to overestimate invasion of the surrounding organs and vessels was seen [515].

Photodynamic therapy of intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasm (IPMN) of the main pancreatic duct is usually treated by surgical excision of the affected pancreas. Nonoperative ablative therapies have not been described. It was treated IPMN of the pancreatic duct with photodynamic therapy (PDT) in a patient who was a poor operative candidate. Porfimer sodium was administered intravenously, and laser light was delivered by a diffusing catheter placed in the pancreatic duct during endoscopic retrograde cholangiopancreatography (ERCP). Imaging and biopsy findings of IPMN resolved after PDT, and symptoms also resolved. Metastatic cancer was diagnosed 2 years after PDT had been initiated. Pancreatic PDT was well tolerated in this case, and may be a therapeutic option for selected patients with IPMN of the main pancreatic duct [516].

OTHER CYSTIC PANCREATIC TUMORS

The apparent question is how to proceed after the detection of an asymptomatic pancreatic cyst choosing one of the following options: no further investigations, additional imaging ± fine needle aspiration (FNA), surveillance, or surgical/endoscopic treatment. Despite a spectacular improvement in diagnostic modalities in the past decades, differential diagnosis and hence management of pancreatic cysts remain controversial. Most centers have adopted a differential approach with follow up in case of absence of secondary features of malignancy and surgical resection in case of a high suspicion of malignancy. Multiple guidelines have appeared. Cystic lesions of the pancreas comprise of a heterogeneous group of diagnostic entities, some of which are benign such as inflammatory pseudocysts or serous cystadenomas and do not require resection when asymptomatic. Others like mucinous cysts or intraductal papillary mucinous neoplasms (IPMN) have a malignant potential and in these cases surgical resection is often indicated. For this reason an adequate distinction between the various cysts is crucial to optimize management strategy. Different diagnostic methods that could be of value in the differentiation include radiologic imaging techniques such as CT, MR, and endosonography. In addition, fluid aspiration for cytopathology, tumormarkers or molecular analysis is widely used. Different guidelines are available but so far no optimal diagnostic algorithm exists. The majority of neoplastic cysts are represented by mucinous cystic neoplasms (MCNs) (10-49 %) and intraductal papillary mucinous neoplasm (IPMN) (21-33 %). Solid pseudopapillary neoplasms are less common. Other rare neoplastic cystic lesions include cystic neuroendocrine tumors and acinar cell cystadenocarcinomas but these will not be discussed in this paper. Many patients with cystic lesions of the pancreas present without abdominal complaints. Lesions are often detected when a radiologic examination is performed for another reason or when an individual decides to undergo preventive screening investigations. When the pancreatic cyst is symptomatic, patients may present with epigastric pain, postprandial fullness, palpable mass, gastric outlet obstruction, nausea, vomiting, diarrhoea, steatorrhea, and/or weight loss. When an advanced cystic neoplasm exists, patients often present with complaints similar to pancreatic adenocarcinoma such as pain, weight loss, and jaundice. Patients presenting with pancreatic cysts have to be thoroughly evaluated. Cross-sectional imaging should be used for the morphological characterization, and EUS-FNA for fluid and tissue sampling could be used in particular cases to discriminate between mucinous and nonmucinous cysts. Management should be based upon on carefully weighting the malignant potential of a pancreatic cystic lesions and the risk of surgery. Larger prospective studies with longer follow up are needed to increase the knowledge of the natural history of pancreatic cysts [517].

Pancreatic cystic lesions (PCLs) represent an increasingly common diagnostic and therapeutic challenge. A significant number of pancreatic cysts are detected incidentally when noninvasive abdominal imaging is performed for an unrelated diagnosis. The vast majority of PCLs are cystic neoplasms (60 %), while injury or inflammation-related cysts (e.g. pseudocysts) account for approximately 30 percent of PCLs. The remaining PCLs are congenital or miscellaneous cysts. Neoplastic cysts include intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs), neoplasms pseudopapillary (SPNs), cvstic endocrine neoplasms. solid ductal adenocarcinomas with cystic degeneration and acinar-cell cystic neoplasms. Since the management of PCLs is a function of cyst type, reliable differentiation between the five most common diagnoses - pseudocyst, IPMN, MCN, SCN and SPN - is of vital importance. Although a number of characteristic imaging features have been reported, many PCLs, especially those with diameter <2 cm, are extremely difficult to differentiate by imaging. Differentiation of low-risk lesions and high-risk lesions is also difficult. Low-risk lesions (pseudocysts, SCNs, congenital cysts and lymphoepithelial cysts) are generally not resected because they have no risk or an extremely low risk of malignant transformation. High-risk lesions are mucin-producing tumors (MCNs and IPMNs) and some cystic variants of solid

tumors (e.g. ductal adenocarcinomas with cystic degeneration). Depending on the degree of dysplasia, MCNs and IPMNs are classified as MCN/IPMN with low- or intermediate-grade dysplasia, MCN/IPMN with high-grade dysplasia and MCN/IPMN with an associated invasive carcinoma. Endoscopic ultrasound (EUS) has been used to image the pancreas with improved resolution. Owing to the pancreas lying directly adjacent to the stomach, an EUS transducer can be placed in close proximity to the pancreas, and the entire gland can be readily imaged. However, the accuracy of EUS morphology in the differentiation of PCLs is not satisfactor. In differentiating mucinous from nonmucinous lesions, the accuracy of EUS morphology was 51 percent. In another study, the level of accuracy of EUS morphology to differentiate between all types of PCLs was 73 percent. The use of EUS-guided fine-needle aspiration (EUS-FNA) for fluid collection has enabled endoscopists to use tumor marker levels and cytology to supplement EUS imaging. The carcinoembryonic antigen has been reported to be the most accurate marker to distinguish nonmucinous from mucinous PCLs. Despite these advances, the accuracy of EUS and cyst fluid analysis for differentiation between mucinous and nonmucinous PCLs, and between benign and malignant PCLs, still remains modest [518].

Cystic pancreatic neoplasms are often an incidental finding, the frequency of which is increasing. The understanding of such lesions has increased in recent years, but the numerous types of lesions involved can hinder differential diagnosis. They include, in particular, intraductal papillary mucinous neoplasms (IPMN), serous cystic neoplasms (SCN), and mucinous cystic neoplasms (MCN). Knowledge of their histological and radiological structure, as well as distribution in terms of localization, age, and sex, helps to differentiate such tumours from common pancreatic pseudocysts. Several types of cystic pancreatic neoplasms can undergo malignant transformation and, therefore, require differentiated radiological management. One review aimed to develop a broader understanding of the pathological and radiological characteristics of cystic pancreatic neoplasms, and provide a guideline for everyday practice based on current concepts in the radiological management of the given lesions [519].

Incidence

To date only a few studies have been performed investigating the true prevalence of pancreatic cysts. It has recently published a study in which 2803 magnetic resonance imaging (MRI) examinations were retrospectively reviewed in a group of mostly asymptomatic patients who decided to undergo a preventive screening abdominal MRI at their own initiative and costs without referral of a physician. Prevalence was 2.4 percent and increased with age. In another study it was reported a prevalence of 2.6 percent. In retrospect, 2832 consecutive computed tomography (CT) scans were reviewed. Patients with known pancreatic disease or symptoms related to the pancreas were excluded. A prevalence of 13.5 percent was found in another recent retrospective study in 616 patients using MRI. Patients were excluded from this study if they had a known or suspected history of pancreatic disease. In all these studies increasing age correlated with a higher prevalence of pancreatic cysts. In an older Italian study reports of 24,039 MRI and CT scans were retrospectively reviewed with a computerized search. Pancreatic cysts were reported in 1.2 percent of which 58 percent (0.7% of total study population) did not have a history of pancreatitis. The highest prevalence of pancreatic cysts using a radiologic imaging technique was found in a study with spin-echo MR images of 1444 patients were reviewed for pancreatic cysts by two radiologists, and pancreatic cysts were described in 19.6 percent of patients. Patients with known history of pancreatic disease were not excluded from this study. In an autopsy study of 300 cases a stunning 24.3 percent were found to have pancreatic cysts. It is of note that this study was performed in elderly patients (more than 80% were older than 65 years), and no information was provided of a possible history of

pancreatic disease. The broad range of prevalence values can be explained by the fact that studies differed in the selection of the study population, in-hospital or out-patient based and whether patients with potential pancreatic disease were excluded from analysis. Importantly, studies also differed in which imaging modality was employed with each technique having its distinct sensitivity and specificity for detecting cysts [517].

Rate of growth

The authors sought to determine magnetic resonance/magnetic resonance cholangiopancreatography (MR/MRCP) imaging features of incidentally discovered benign, noncommunicating cystic neoplasms (BNCNs) of the pancreas to assess their evolution over time and identify MR/MRCP imaging features predictive of tumour growth. It was a retrospective study, so informed consent was waived. Sixty-two patients with a diagnosis of BNCN were assessed. Inclusion criteria were incidentally discovered cystic neoplasm of the pancreas with nonmeasurable walls, no mural nodules and no communication with the pancreatic ductal system and who underwent ≥1 MR/MRCP examination. Image analysis, performed at diagnosis and during follow-up, included macroscopic pattern (microcystic/ macrocystic/mixed), number of cysts (unicystic/oligocystic/multicystic), BNCN maximum diameter and tumour growth rates. A total of 64 BNCNs was detected. Macroscopic pattern was mixed in 31/64 (48 %), microcystic in 28/64 (44 %) and macrocystic in 5/64 (8 %). BNCNs appeared multicystic in 38/64 (59 %) cases, oligocystic in 22/64 (35 %) and unicystic in 4/64 (6 %). All qualitative parameters remained unchanged during follow-up. At diagnosis, the median maximum BNCN diameter was 35 mm and 38 mm at the final examination. BNCNs showed a tumour growth rate of 2 mm/year. Mixed and microcystic patterns were the most common, accounting for 48 percent and 44 percent of cases, respectively, and showed no change over time. MR/MRCP features predictive of lesion enlargement were a mixed/ macrocystic pattern, and lesion size was >3 cm. Factors influencing receptivity to future screening options for pancreatic cancer in those with and without pancreatic cancer family history [520].

Diagnostics

Diagnostic methods that can be valuable in the differentiation of pancreatic cysts include radiologic imaging techniques such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Endoscopic ultrasonography (EUS) and EUSguided fine needle aspiration (EUS-FNA) for cytopathologic examination, tumormarker determination. and molecular analysis are also widely used. Transabdominal ultrasonography is a safe imaging technique without radiation exposure which is helpful in the differentiation of solid and cystic lesions. It is currently widely used in the evaluation of abdominal complaints. As a result, cystic lesions are often initially detected with this modality. It is however not the imaging of first choice since it is difficult to visualize the complete pancreas due to overlying bowel or fat, and it is rather operator dependent. CT is often used in the diagnostic workup. It is a widely used imaging technique to visualize and differentiate pancreatic cysts based on morphologic features as size, microcystic/macrocystic aspect, presence of septations, nodules, and calcifications. MRI has the additional advantage to show a possible connection with the pancreatic duct which on T2-weighted image sequences is better visualized than with CT. Another advantage of MRI, especially for follow up of the cysts, is the lack of radiation exposure. EUS has emerged as a useful diagnostic technique in the evaluation of pancreatic cystic lesions, providing fine detail on the characteristics of the cyst because of the very high spatial resolution. It has therefore been suggested as an ideal imaging technique for pancreatic cysts. EUS can image characteristics of the cysts as well as the parenchymal changes and has a role in determining the resectability if malignancy is

present. Despite the fact that EUS is presently widely used for the differential diagnosis, a number of points of discussion still exist. Since EUS is invasive, technically difficult, and expensive, it is not available in all hospitals. Furthermore there is a substantial interobserver agreement between endosonographers. An advantage of EUS is the possibility to perform FNA for analysis of the cyst fluid. EUS-FNA is considered a safe technique to obtain pancreatic cyst fluid with rare, mostly mild complications, but infection, pancreatitis, and intracystic haemorrhage have been reported. Infection of cysts after FNA is rare and, although common practice in most centers, data are lacking to support the use of prophylactic antibiotics. Furthermore, to minimize the risks of subsequent infection one should keep the number of punctures to a minimum and attempt to aspirate all fluid from the cyst whenever possible [517].

Cyst fluid analysis

Pancreatic cyst detection is increasing largely due to increasing use of cross-sectional imaging. The management of pancreatic cysts differs for true cysts, pseudocysts, mucinous cysts, nonmucinous cysts, and malignant lesions. Depending on the setting, diagnostic tests, such as cross-sectional imaging, endoscopic ultrasound, cyst fluid chemistry, and cytology, have moderate accuracy in characterizing the cyst subtype. Molecular analysis of cyst fluid aspirates has shown promise in preliminary studies and may require smaller fluid volumes than is needed for carcinoembryonic antigen level and cytology. One article reviewed published studies in which molecular analysis was performed in the evaluation of pancreatic cysts. The molecular studies are compared with the conventional tests. Most studies have had moderate sample sizes (16-124) and have characterized a high proportion of patients with malignant cysts. Evaluation of molecular analysis as a diagnostic tool merits larger prospective trials with long-term follow-up of patients who are not sent to surgery. Larger cysts may meet size criteria for resection, and it is the smaller cysts for which molecular analysis may be of benefit if additional molecular testing results in a change in management [521].

Cytological evaluation of pancreatic cyst fluid is widely used, and several studies report a sensitivity of approximately 50 percent for the differentiation of mucinous and nonmucinous pancreatic neoplasms. However, other studies show less positive results since cytopathology is often nondiagnostic due to the low cellularity of the obtained cyst fluid. Biochemical analysis of cyst fluid and tumor markers have been evaluated for several years with the underlying thought that markers secreted into the cyst fluid identify the epithelial lining. Amylase is usually elevated in pseudocysts and IPMNs and low in MCNs and serous cystadenomas. Of the tumor markers, CEA is considered the best discriminant marker to differentiate between a mucinous and a nonmucinous cyst. A low CEA level (<5 ng/mL) has been shown to have a sensitivity between 50 and 100 percent and a specificity of 77-95 percent to differentiate between mucinous and nonmucinous cysts. Pseudocysts and serous cystadenomas generally have a low CEA value. Currently, the most widely used cutoff for an elevated CEA is 192 ng/mL. Altogether, the current yield of FNA is small, which can be caused by the microcystic aspect of a cyst, the high viscosity of the fluid or the minimum amount of fluid that is needed for certain examinations of the fluid. The standard use of a 19 G needle could be helpful to aspirate both larger cysts and cysts which contain fluid with a high viscosity. New methods to improve the yield of FNA are urgently required. Existing tumor markers have only limited value, and more sensitive biomarkers need to be identified. New techniques including proteomics and molecular analysis may be helpful for the differential diagnosis of pancreatic cysts. Also the development of new techniques to minimize the fluid needed for examinations may well be useful. Furthermore, the development of new techniques to increase the cellularity of the obtained fluid could be helpful. Three reports have been recently published, studying a new type of brush (EchoBrush, Cook Medical) to improve the yield of cytologic examination. These studies suggest that this relatively new technique improves the yield, but larger randomized trials are

necessary to confirm these results and to define the safety profile of this more aggressive approach [517].

It was the aim of one study to examine pancreatic cyst cases that lack markedly atypical or malignant epithelium on endoscopic ultrasound-guided fine-needle aspirations. It was conducted a retrospective case review study, including 24 cases that were either acellular or lacked cytologic atypia and were subsequently resected. The cases were retrospectively divided into 3 categories: non-diagnostic, cyst contents only, and cyst contents with blandappearing epithelium. The cyst contents were subdivided into mucinous and non-mucinous types. The cytologic diagnoses were correlated with cyst fluid carcinoembryonic antigen (CEA) levels and subsequent histologic diagnoses. Category 1 comprised 4 cases: 2 cases (CEA >800 ng/ml) with mucin-producing neoplasms and 2 cases (CEA not determined) with microcystic serous cystadenomas. Category 2 included 4 cases with non-mucinous and 4 with mucinous contents. In the first subgroup, 2 cases (CEA >800 ng/ml) showed mucinous cystic neoplasms and 2 cases (CEA negligible or not determined) pseudocysts. In the second subgroup, there were 3 cases with neoplastic mucinous cysts (1 CEA >800 ng/ml, 2 not determined) and 1 case with a lymphoepithelial cyst with mucinous metaplasia (CEA >800 ng/ml). Almost all cases (10/11) in category 3 had neoplastic mucinous cysts regardless of the CEA levels. The proposed 3 cytologic categories of pancreatic cystic lesion combined with cyst fluid CEA levels provide useful clinical information [522].

Contrast-enhanced ultrasound

The aim of one study was to evaluate the added value of contrast-enhanced ultrasound (CEUS) in the pancreatic cystic mass (PCM) diagnosis by using a qualitative and quantitative analysis in order to make a relevant characterization. Between 2008 and 2011, 37 patients with PCM discovered at ultrasound examination were prospectively followed. A qualitative and quantitative CEUS analysis was performed in order to differentiate etiologies of the PCM. In the quantitative analysis several parameters were followed: Peak intensity (PI), time to peak (TTP), maximum ascending gradient (GRAD), time to maximum gradient (TTG) and area under the curve (AUC). Normalized ratios were also calculated. In all patients a definite cytological or histological diagnosis was obtained. Thirty-seven patients were studied: 12 with pancreatitis-associated pseudocyst and 25 with cystic tumors (10 serous cystic adenoma, 5 mucinous cystic adenoma, 6 cystadenocarcinomas, 2 solid pseudopapillary tumors and 2 intraductal papillary mucinous neoplasms). There was a significant difference of the nAUC and nTTP between pseudocyst and cystic tumors. A normalized TTP value above 7 sec was suggestive for the diagnosis of pseudocysts with 79 percent accuracy. There was a significant difference of nTTP and nTTG between the benign and malignant lesions. nTTP < 9 sec and nTTG < 8.5 sec rules out malignant cysts in almost 90 percent of cases. Thus, the CEUS is useful in the diagnosis of PCM. The quantitative analysis of the enhancement of the cystic wall may discriminate the different types of the PCM [523].

СТ

To assess the value of multi-slice computed tomography (MSCT) in the diagnosis and differential diagnosis of pancreatic mucinous cystic neoplasms and serous cystadenoma the MSCT images were reviewed for 19 pathologically confirmed cases of pancreatic mucinous cystadenomas and 13 cases of pancreatic serous cystadenomas (n=13) treated in our center between 2003 and 2009. The CT features were analyzed including the tumor location, contour, dimension of the largest cyst, cystic wall, septation, presence of calcification, solid component, pancreatic atrophy, main pancreatic duct dilatation, and lesion margins. Significant differences were found between the two groups in lesion diameter, cyst distribution of the largest cyst (>2 cm), and the presence of solid component. It was

concluded that MSCT can be of important value in the diagnosis and differential diagnosis of pancreatic mucinous cystic neoplasms and serous cystadenomas [524].

MRI

To assess the degree of interobserver agreement of MRI in the diagnostic assessment of pancreatic cysts (PCs) magnetic resonance imaging sets of images of 62 patients with PCs (32 with histological confirmation and 30 with clinical diagnosis) were reviewed by 4 experienced radiologists. Features scored included septations, nodules, solid components, pancreatic duct communication, and wall thickening (>2 mm). Radiologists were asked whether they considered the PC mucinous and if the PC was suspicious for malignancy. Furthermore, they had to choose a classifying diagnosis. Intraclass correlation coefficient (ICC) was used to measure agreement within the group. Interobserver agreement for septations and nodules was fair (ICC, 0.36 and 0.23, respectively). Agreement for the presence of solid components was fair (ICC, 0.23), agreement for communication with the pancreatic duct was moderate (ICC, 0.53), and agreement for wall thickening was moderate (ICC. 0.44). There was fair agreement for the discrimination between mucinous and nonmucinous PC (ICC, 0.36). Agreement was fair (ICC, 0.26) for a classifying diagnosis and fair for the presence of malignant features (ICC, 0.33). It was concluded that interobserver agreement was poor to moderate for individual PC features, and there was fair agreement for a classifying diagnosis. Magnetic resonance imaging morphology alone did not allow for a reliable discrimination between different types of PC [525].

To determine the utility of 3.0-Tesla diffusion-weighted (DW) magnetic resonance imaging (MRI) for focal cystic pancreatic lesion (FCPL) characterization 55 FCPL (34 IPMN, 5 serous cystadenoma, and 16 inflammatory) were evaluated. Two radiologists reviewed in consensus DW-MRI images. Reference standard was obtained from patient history, cytological and histopathology data, FCPL fluid analysis, and follow-up imaging results. Signal intensity (SI) and apparent diffusion coefficient values (ADC) of FCPL and normal pancreas were measured. FCPL-to-pancreas SI and ADC ratios were also calculated. Qualitatively, 11 of 21 non-mucinous vs. 4 of 34 mucinous lesions appeared hyperintense at b value of 1,000 s/mm². Three FCPL demonstrated restricted diffusion: all inflammatory. Significant differences in mean ADC between neoplastic versus non-neoplastic, and mucinous versus non-mucinous (P = 0.013) lesions were demonstrated. FCPL-to-pancreas ADC and SI ratios demonstrated significant differences between neoplastic versus non-neoplastic lesions and mucinous versus non-mucinous lesions. It was concluded that although mean ADC values and FCPL-to-pancreas SI and ADC ratios may be helpful in differentiating FCPL, characterization of individual FCPL by means of 3.0-Tesla DW-MRI appears limited [526].

High-resolution optical imaging

High-resolution optical imaging has recently been investigated for differentiating between morphologic features of pancreatic tissue. This includes both confocal endomicroscopy (CEM) and optical coherence tomography (OCT). CEM is a micron-scale optical imaging technique that provides powerful imaging features with subcellular resolution that complement, rather than replace, the use of conventional white-light endoscopy. Previously, in vivo use of CEM was limited owing to the inability to reduce the optics and the scanning mechanism to an endoscope-compatible size. As confocal instrumentation technology advances, submillimeter CEM probes will become available and new advancements in gastrointestinal imaging are being made. CEM use for imaging pancreatic cysts has been reported in a small pilot study. Pancreatic cysts and solid masses were investigated in this study. Although some technical challenges related to high-specular reflections degrading image quality were encountered, this study was quite successful and technical feasibility for performing micron-scale imaging with CEM during a pancreatic EUS-FNA procedure was

achieved for the first time. However, although very promising, the main drawbacks of CEM are the reduced imaging depth and field of view, both being limited to several hundred microns. Therefore, CEM might not be able to reliably identify morphologic differences between the microcystic walls of the serous and mucinous cysts. Nevertheless, its capability for visualizing tissue morphology at the subcellular level can be further exploited for differentiating between various cystic lesions of the pancreas, as well as between autoimmune pancreatitis (AIP) and SPNs. The differentiation between AIP and SPNs is particularly important because AIP can produce pancreatic masses that resemble pancreatic carcinoma both clinically and radiographically. While the neoplasms are usually managed by surgical resection, pancreatitis is managed nonsurgically [518].

OCT is an interferometric high-resolution optical imaging technique and therefore it enables tissue imaging at depths that far surpass CEM capability. Up to 2 mm imaging depth is possible with OCT, depending on the tissue structure. In addition, OCT has the potential to image tissue structures at the scale of several microns and produce cross-sectional or en face images that resemble a histology slide. However, OCT imaging at the subcellular level has not yet been demonstrated. Both ex vivo and in vivo studies have demonstrated the capability of this technique to identify and recognize the gastrointestinal and pancreaticobiliary wall structure, as well as to differentiate between the wall structure and cystic fluid scattering properties of serous and mucinous cysts. Key imaging features of the mucinous cystic lesions were the high scattering of the mucinous fluid and the presence of a large amount of homogenous high-scattering tissue between the microcysts that corresponds to the intervening fibrocollagenous tissue, as well as the increased epithelial thickness of the malignant cysts. The OCT images of the serous cysts showed multiple tiny cysts with welldefined outlines. The thin septae between the cysts showed homogenously high scattering, creating a honeycomb appearance. Significantly, OCT images also showed that the serous cyst content is homogenously dark and lacked scattering effect. Strong correlations between histology and OCT images of serous and mucinous cysts were also found. Based on these correlations, OCT criteria for differentiating between these two classes of cysts were developed. The cysts were determined to be mucinous or nonmucinous based on preestablished OCT criteria and the results were compared with histology findings. Despite modest training and little experience with OCT imaging, the clinicians were able to identify mucinous cysts with high levels of accuracy (96-100 %). Thus, high-resolution optical imaging may be a suitable tool for complementing EUS findings and help clinicians to more reliably differentiate between various cystic lesions of the pancreas. Cystic wall morphology and scattering properties of the cystic fluid may be the main cystic features that can be exploited by OCT. The thickness and the cellular appearance of the cystic epithelium could be investigated by CEM. Therefore, high-resolution optical imaging may play an important role in the diagnosis of cystic lesions of the pancreas, as well as in other organs [518].

Immunohistochemistry

The recent World Health Organization classification for tumors of the digestive system defined grossly and histologically hepatic mucinous cystic neoplasms and intraductal papillary neoplasms of the bile duct separately. In one study, the immunohistochemical features of intraductal papillary neoplasm of the bile duct (19 cases) and hepatic mucinous cystic neoplasm (5 cases) were characterized and compared with those of similar pancreatic lesions, intraductal papillary mucinous neoplasm of the pancreas (12 cases), and pancreatic mucinous cystic neoplasm (6 cases) and with those of other biliary cystic lesions, peribiliary cysts (10 cases). Intraductal papillary neoplasm of the bile duct and intraductal papillary mucinous neoplasm of the pancreas frequently expressed cytokeratin 7; mucin core proteins 1, 2, 5AC, and 6; trypsin; and amylase. Hepatic and pancreatic mucinous cystic neoplasms frequently expressed cytokeratin 7, mucin core proteins 1 and 5AC, estrogen receptor,

progesterone receptor, trypsin, and amylase. Estrogen and progesterone receptors were expressed in the subepithelial stromal cells. The groups with intraductal papillary neoplasm of the bile duct and intraductal papillary mucinous neoplasm of the pancreas were different from the groups with hepatic and pancreatic mucinous cystic neoplasm with respect to several phenotypes reflecting gastric and intestinal metaplasia and also the lack of expression of estrogen and progesterone receptors. The Ki-67 and p53 labeling indexes increased significantly with the malignant progression of intraductal papillary neoplasm of the bile duct and intraductal papillary mucinous neoplasm of the pancreas. The p16 labeling index decreased and EZH2 labeling index increased significantly with the malignant progression of intraductal papillary neoplasm of the bile duct and intraductal papillary mucinous neoplasm of the pancreas. In conclusion, intraductal papillary neoplasm of the bile duct and hepatic mucinous cystic neoplasm might be regarded as biliary counterparts of intraductal papillary mucinous neoplasm of the pancreas and pancreatic mucinous cystic neoplasm, respectively, and the mucinous cystic neoplasm and intraductal papillary neoplasm groups differed from each other. Labeling indexes of Ki-67, p53, p16, and EZH2 were comparable in intraductal papillary neoplasm of the bile duct and intraductal papillary mucinous neoplasm of the pancreas along with their malignant progression, suggesting a common carcinogenic process of the tumors [527].

Microcystic adenoma

Serous cystic neoplasms of the pancreas are generally considered benign lesions. Malignant counterparts have been occasionally described, and the diagnosis of malignancy is based solely on the presence of synchronous or metachronous metastases to the lymph nodes or liver, direct tumor invasion into adjacent organs, or vascular invasion. However, these malignant serous cystic tumors are lined by benign-appearing glycogen-rich cuboidal cells, which have been morphologically indistinguishable from benign microcystic serous cystadenoma in all the cases reported so far. It was reported a unique case of microcystic serous signet ring-like cells and solid nests. It was believed that this case represents the first case of a cytologically malignant neoplasm arising from a benign serous cystadenoma (carcinoma ex microcystic serous cystadenoma) [528].

Pancreatic serous cystadenomas are benign cystic neoplasms. Extensive degeneration mimicking a pancreatic pseudocyst has been described in several types of pancreatic neoplasms but has not been documented in serous cystadenomas. It was reported subtotal cystic degeneration of microcystic serous cystadenomas (MSCA) that produces radiographic, gross, and microscopic overlap with pancreatic pseudocyst. Resected MSCA with degenerative change were identified from the pathology archives. The clinical, radiographic, gross, and microscopic findings were reviewed. Eight MSCAs with subtotal cvstic degeneration were retrieved from among 397 resected serous cystadenomas (2 %). There were 2 men and 6 women (mean age, 52 years). Available radiographic studies showed classic features of MSCA in 2 of 4 cases. Four cysts were unilocular, and 4 were multilocular. Gross features of MSCA were noted focally in the multilocular cases but were not evident in the unilocular examples. The predominant histologic features were those of pancreatic pseudocyst, including a fibrotic cyst wall lacking epithelium and instead composed of myofibroblastic proliferation, hemorrhage, and inflammation. Residual foci of MSCA were embedded in fibrosis, comprising 5 to 60 percent of the tumor volume. Most pancreatic serous cystadenomas display characteristic morphology, including a glycogen-rich epithelial lining and prominent subepithelial capillaries; however, extensive degenerative macrocystic change can obscure these classic features. This phenomenon is to be distinguished from macrocystic serous cystadenoma, in which thin-walled macrocystic spaces are epithelium

lined. Thus, serous cystadenoma should be included in the differential diagnosis of pancreatic masses with extensive degenerative cystic change [529].

Serous oligocystic adenoma

The purpose of one study was to describe the MRI features of the benign pancreatic neoplasm serous oligocystic adenoma (SOA) that differ from those of mucinous cystic neoplasm (MCN), a neoplasm with the potential for malignant degeneration. Seven patients with SOA (seven women; mean age 37 years) and eight patients with MCN (eight women: mean age 40 years) were included. Several imaging features were reviewed: mass size, location, shape, wall thickness, cyst configuration (Type I, unilocular; Type II, multiple clustered cyst; Type III, cyst with internal septation) and signal intensity of the lesion with heterogeneity. SOA lesions were smaller (3.4 cm) than those of MCN (9.3 cm). The commonest lesion shape was lobulated (86 %) for SOA, but oval (50 %) or lobulated (38 %) for MCN (p=0.015). The most common cyst configuration was Type II (85.7%) for SOA and Type III (75 %) for MCN. Heterogeneity of each locule in T(1) weighted images was visible in all cases of MCN, but in no case for SOA. SOA could be differentiated from MCN by identifying the imaging features of lobulated contour with multiple clustered cyst configurations and homogeneity of each locule in T(1) weighted MR images [530].

Growth rate

The natural history and growth pattern of pancreatic serous cystic neoplasms (SCNs) are not well understood. One study was designed in order to get insight into the growth rate of SCNs and to suggest recommendations for their management. Patients with well-documented incidentally discovered or minimally symptomatic SCNs who underwent yearly surveillance MRI were analysed using a linear mixed model. The growth rate and the effects of different fixed factors (sex, personal history of other non-pancreatic malignancies, radiological pattern, clinical presentation, tumour site) and random factors (age and tumour diameter at the time of diagnosis) on tumour growth were investigated. Study population consisted of 145 patients. Estimated overall mean growth rate was 0.28 cm/year, but the growth curve analysis showed a different trend between the first 7 years after the baseline evaluation (growth rate of 0.1 cm/year) and the subsequent period (years 7 to 10, growth rate of 0.6 cm/year). Tests for fixed effects demonstrated that an oligocystic/macrocystic pattern and a personal history of other tumours are significant predictors of a more rapid mean tumour growth (growth rates of 0.34 cm/year). Furthermore, tumour growth significantly increased with age. Overall, SCNs grow slowly, and an initial non-operative approach is feasible in all the asymptomatic or minimally symptomatic patients. The oligocystic/macrocystic variant, a history of other non-pancreatic malignancies, and patients' age impact on tumour growth. In any case, a significant growth is unlikely to occur before 7 years from the baseline evaluation. Tumour size at the time of diagnosis should not be used for decisional purposes [531].

Serous cystadenoma

Patients with serous cystadenomas (SCNs) are predominantly elderly women with a median age of approximately 60 years, and the cysts can arise in any region of the pancreas. Classical features of a serous cystadenoma include microcystic morphology, a central area of calcification, and a watery, nonviscous fluid content. However a macrocystic variant of serous cystadenomas exists and can easily be confused with a pseudocyst or a mucinous cystadenoma. Serous cystadenomas are lined by a glycogen-rich cuboidal epithelium which can be shown with cytopathological analysis. Although a small number of cases of malignant serous cystadenomas have been described, it is generally believed that serous cystadenomas have virtually no malignant potential. Serous cystadenomas can be treated

conservatively if the patient is asymptomatic. Surgery is treatment of choice when a patient has symptoms or the distinction between a serous cystadenoma and a mucinous cystic neoplasm is not possible [517].

To evaluate the washout (WO) pattern of serous cystadenomas (SCAs) compared with endocrine tumors (ETs) and intraductal papillary mucinous neoplasm (IPMN) patients with serous cystadenoma (n=12), ET (n=29), and IPMN (n=35) underwent 4-phase computed tomography CT. Tumors were categorized as hyperdense or hypodense. Computed tomographic values measured were unenhanced attenuation (AU), pancreatic attenuation (A12, 12 seconds), portal attenuation (A35), and equilibrium (A158). Computed tomographic parameters calculated were wash-in (WI) = A12 - AU; WO = A12 - A35; and washout ratio (WOR) = WO/WI × 100/22. Hyperdense SCAs had significantly higher WOR than did hyperdense ETs. Among the 3 hypodense tumors, SCAs had the significantly highest WOR. Relative to the pancreas, the WOR of SCAs were equivalent, whereas the WOR of ETs and IPMNs were significantly lower. It was concluded that hyperdense SCAs had significantly highest WOR than did hyperdense ETs, and hypodense SCAs had the significantly highest WOR among the three [532].

Serous cystadenoma coexistent with adenosquamous carcinoma

A 70-year-old man was admitted to our hospital because a mass was incidentally found in the body of the pancreas. The mass was suspected to be serous cystadenoma from the findings of abdominal enhanced computed tomography, magnetic resonance imaging and endoscopic ultrasonography. In addition, another solid mass was detected in the pancreatic head on imaging tests. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography showed stenosis both of the main pancreatic duct at the head and bile duct, but the brushing cytology of the bile duct at ERCP showed no malignant cells. However, the findings of several examinations strongly suggested the coexistence of a serous cystadenoma and a pancreatic cancer, therefore we conducted spleen-preserving total pancreatectomy, and the pathological findings of the resected specimen showed serous cystadenoma coexistence with pancreatic adenosquamous carcinoma [533].

Solid cystic serous adenoma

To differentiate between solid serous cystadenoma (SSCA) and endocrine tumor (ET) of the pancreas using dynamic CT findings a study was performed. Between 2001 and 2008, there were 3 SSCA and 15 ET surgically resected in our institute, for whom preoperative multidetector-row CT were available. Various CT features were retrospectively evaluated by two radiologists in consensus for the differentiation between the two entities. Delay time for early and delayed phase images were 40 and 180 or 240s, respectively. For qualitative assessment, density of the tumors relative to the surrounding parenchyma was evaluated, along with other characteristic features. In patients for whom digital data were available, CT values of the tumors were measured, and quantitative assessment was also performed. Relative and absolute washout rate (RWR and AWR, respectively) were also calculated. Mean sizes of the two groups were similar. Tumors were seen as low density area more frequently in SSCA than in ET on unenhanced CT (3/3 vs 1/14), and also on the delayed phase image (2/3 vs 0/14). Fibrous capsule was observed more frequently in SSCA (2/3) than in ET (0/14). CT value of the tumor on unenhanced CT was significantly lower, and RWR was higher in SSCA than in ET. The difference in delayed phase CT density and AWR did not reach statistically significant level. It was concluded that unenhanced and enhanced CT findings may be of value in differentiation between SSCA and ET [534].

Serous cystadenocarcinoma

Serous adenomas represent 1-2 percent of pancreatic neoplasms and typically are asymptomatic not requiring any treatment and simple observation is the option of choice. Although, they carry a realistic risk of malignancy despite the general view that they never become malignant. It was reported a case, which, according to the best knowledge is the 27th case reported in the literature. A 86-year old patient known to have a serous cystadenoma of the pancreas treated conservatively through a close clinical and radiological follow up which was unattended for 4 years ending up to our emergency department suffering an acute abdomen. Exploratory laparotomy revealed a perforated prepyloric ulcer which was treated accordingly. Patient died some weeks later due to severe medical co morbidities. It was summarized that serous cystic neoplasms of the pancreas carry a realistic risk of malignancy despite the general view that they never become malignant. In our opinion the treatment strategy of serous cystic neoplasms of the pancreas should be aggressive even in cases of remote metastases since prognosis of the disease is satisfactory [535].

Mucinous cystadenoma

Patients with MCNs are almost exclusively middle-aged women, and most of the MCNs appear in the body or tail of the pancreas although they occasionally may occur in the head. The average size of the cysts is larger than 5 cm at time of presentation. MCNs are generally macrocystic, thick-walled cysts that typically lack communication with the ductal system. A microcystic MCN is rarely seen. They are either unilocular or multilocular with a small number of compartments. Unique is the fact that MCNs contain a mucinous, dense ovarian stroma surrounding the epithelial cells, which is never seen in other cystic lesions. Therefore, ovariantype stroma is considered a requisite to distinguish MCNs from the other cystic neoplasms [517].

Mucinous cystadenoma of the mesocolon

Mucinous cystadenomas are tumors arising mostly from the ovaries and pancreas. They can also arise from the kidneys, lungs, liver and appendix, but are rarely seen in the mesocolon. Recently, they have been included in an updated classification of mesenteric cysts and cystic tumors. The WHO classification divides them into three subcategories according to their malignant behavior. Onereport of two cases of mucinous cystadenoma of the mesocolon discusses the diagnostic and therapeutic modalities as well as the pathophysiological pathway(s) of development of these neoplasms. The diagnosis of mucinous cystadenomas of the mesocolon is challenging due to the absence of specific clinical, biological and radiological features, and is often made during or after laparotomy. Preoperative biopsy is not useful and may even lead to misdiagnosis or peritoneal spillage. Surgery is the only curative treatment, but the modalities of resection are still a subject of debate [536].

Von Hippel-Lindaus disease

von Hippel-Lindau (vHL) disease is a rare condition that leads to characteristic lesions within many different body systems. Pancreatic manifestations of vHL cover a wide spectrum of pathologies, and thus, accurate characterization and management is critical. A comprehensive and systematic text word and MeSH search of the medical literature was performed to identify studies where information regarding the prevalence, clinical characteristics, and management recommendations could be extracted. Eleven studies were identified but 2 studies utilized the same data set. Of the 10 remaining studies, a total of 1,442 patients with vHL were available for analysis. Four hundred and twenty patients were

examined for any type of pancreatic lesion, 362 for simple cysts or serous cystadenomas (SCAs), and 1,442 for neuroendocrine tumors (NETs). Of the 420 assessed for any pancreatic manifestation of vHL, 252 (60 %) had a pancreatic lesion identified. Simple cysts that present as the sole manifestation of pancreatic disease were common and found in 169 of 362 (47 %) patients. These are usually asymptomatic and do not normally require intervention. SCAs were reported in 39 of 362 (11 %) patients and followed a similar benign course; resection is acceptable in symptomatic patients. NETs were identified in 211 of 1,442 (15 %) patients, and 27 of 1,442 (2 %) lesions behaved malignantly. Management of NETs depends on size, doubling time, and underlying genetics. Renal cell carcinoma is a characteristic in vHL, but there were no cases of pancreatic metastases identified from the included studies. Adenocarcinomas of the pancreas are not pathogenically linked to vHL. Simple cysts and SCAs are benign, but NETs require careful observation due to their malignant potential [537].

Von Hippel-Lindau disease is an autosomal dominant genetic disorder characterized by neoplasms developing in multiple organs. Although the pancreas is one of the most frequently involved organs, the frequency of pancreatic cysts, cystadenomas, neuroendocrine tumors and diabetes has not been sufficiently evaluated due to the low prevalence of this disease. In one paper, it was reviewed and retrospectively analyzed 11 patients with von Hippel-Lindau disease. Eleven patients (6 males, 5 females) who underwent CT or MRI scans at Okayama University Hospital between 2002 and 2009 were enrolled in this study. Their pancreatic CT scans, MRI scans, biochemical test results and clinical histories were retrospectively reviewed. All patients had one or more pancreatic involvements. Nine of the 11 patients had multiple pancreatic cysts, 2 had dilatation of the main pancreatic duct, 3 had a non-functioning pancreatic endocrine tumor (one patient required pancreatoduodenectomy due to the endocrine carcinoma) and 3 had diabetes mellitus. Pancreatic cystadenomas were not detected in this case series. The prevalence of pancreatic involvement was 100 percent in this study. Regular screening and scheduled follow-up for pancreatic lesions and diabetes should be performed on individuals predisposed to von Hippel-Lindau disease [538].

Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder that results from a germline mutation in the VHL gene. Germline mutations in the VHL gene lead to the development of several benign or malignant tumors, and cysts in many organ systems. The most common site of involvement is the central nervous system (CNS), but renal and pancreatic diseases are also frequent. Hemangioblastoma of the retina and CNS, renal cell carcinoma (RCC), pheochromocytoma, and endolymphatic sac tumors are also common. The most common pancreatic lesion is a simple cyst, but other lesions can also be found including serous cystic neoplasms (SCNs), neuroendocrine tumors (NETs), adenocarcinoma, hemangioblastomas, and renal cell carcinoma metastases. A number of studies have reported the clinical characteristics of these pancreatic tumors. However, few reports of pancreatic cystic lesions and radiological follow up studies using computed tomography (CT) and magnetic resonance images (MRI) have been made. The aim of one study was therefore to assess the prevalence, types of lesions, and in particular the natural history of pancreatic cysts and their impact on the management of patients with VHL. A few previous reports have described pancreatic involvement in VHL patients, with a reported frequency of 17 to 89 percent. It was retrospectively analyzed the medical records and the computed tomography (CT) and magnetic resonance imaging (MRI) findings of 20 VHL patients who were diagnosed between 1996 and 2010 at one hospital. The clinical findings, family history and type of tumors and/or cysts were reviewed for each patient. It was also analyzed the imaging findings for the pancreas in detail. Pancreatic involvement was noted in 16 of the 20 patients (80 %). Eleven patients had multiple cysts diffusely distributed in the pancreas, and one patient had a single cyst in the pancreas head. Two patients had serous cystic neoplasms (SCNs) with multiple cysts, and another two patients had neuroendocrine tumors (NETs) which were conventional radiological findings. The largest cysts of four patients (27 %) increased in size and that of three patients (20 %) decreased in size during the follow-up period. It was performed surgical resections for the pancreatic tumors (one NET and one SCN) and also performed endoscopic treatment for a pancreatic cyst in one VHL patient with obstructive jaundice. None of the patients died as a result of pancreatic disease. The most common type of pancreatic lesions was multiple cysts. SCNs were present in only 10 percent of the VHL patients. The cysts in the study had variable growth rate. Nearly 25 percent of the largest cysts increased in size. But surprisingly, 20 percent of the largest cysts decreased in size. These findings were similar to the results of the study but differed from the other studies. Also, the cysts of each patient had variable growth rate. In half of the patients, positive and negative growing cysts co-existed. Thus, other organ compression because of the presence of a cyst may improve naturally without treatment in some cases. In this study, the outcome of the VHL patients was good, and only one patient died as a result of a hemangioblastoma. The pancreatic cystic lesions did not influence the outcome of the VHL patients [539].

One recent study demonstrated the inverse correlation of expression of S100P and von Hippel-Lindau gene product (pVHL) in pancreatic intraepithelial neoplasia (PanIN) and pancreatic ductal adenocarcinoma (PDA). A new study investigated whether there is a correlation of expression of these two markers in common cystic neoplasms of the pancreas. Immunohistochemical stains for S100P and pVHL were performed on 97 cystic neoplasms of the pancreas, including 23 mucinous cystic neoplasms (MCNs), 39 intraductal papillary mucinous neoplasms (IPMNs), 12 solid pseudopapillary tumors (SPTs), and 23 serous microcystic adenomas (SMAs). The results demonstrated a nuclear and cytoplasmic staining pattern of S100P in 91.3% of MCNs and 100% of IPMNs. In contrast, none of the SPTs or SMAs was positive for S100P. All IPMNs and SPTs, and all S100P-expressing MCNs were negative for pVHL, including 20 MCNs and 20 IPMNs with low-grade dysplasia. All cases of SMA were positive for pVHL. The data suggest 1) the inverse correlation of expression of S100P and pVHL in MCN and IPMN is similar to that in PanIN and PDA, suggesting a role of these two proteins in early tumorigenesis; 2) the loss of pVHL expression in MCN and IPMN supports the recent recategorization of these neoplasms without any cytological atypia as low-grade dysplasia instead of adenoma; 3) the loss of expression of pVHL in SPT supports the concept of an uncertain malignant potential of this entity; and 4) the lack of expression of S100P and expression of pVHL in SMA supports the benign nature of this entity [540].

Incidental pancreatic cysts

It was examined whether the presence of pancreatic cysts could be a risk for pancreatic cancer by comparing the incidence and characteristics of cysts found by magnetic resonance (MR) imaging in patients with and without pancreatic cancer. Half-Fourier rapid acquisition with relaxation enhancement images and MR cholangiopancreatography were performed in 116 patients with pancreatic cancer (PC group) and 1226 with nonpancreatic disease (NP group). Incidence and characteristics of cysts were analyzed. Pancreatic cysts were detected in 65 patients (56 %) of the PC group and in 123 patients (10 %) of the NP group. According to the multivariate analysis, cyst presence was a significant risk factor for pancreatic cancer (odds ratio, OR, 10.3), especially cysts larger than 10 mm (OR 4,7). When the definition of cyst presence in the PC group was restricted to the 33 cases with cysts considered to have existed before the development of cancer, the incidence was still high (OR 3.0) and size remained significant (OR 4.4). Patients with pancreatic cysts, especially larger than 10 mm, were considered to be at an increased risk of pancreatic cancer over the entire pancreas [541].

Nonneoplastic mucinous cysts

An undercharacterized subclass of pancreatic mucinous cysts without histologic characteristics of neoplasia is emerging. One article aimed to highlight the clinical characteristics and implications of this new subset of pancreatic cystic lesions. The clinical. radiologic, and pathologic features of all cysts that underwent operative resection at a tertiary referral pancreatic disease center from 2005 to 2009 were reviewed. Immunohistochemistry for mucinous peptide antigens was selectively performed. Of 104 operations, a pathologic examination revealed 52 intraductal papillary mucinous neoplasms, 9 mucinous cystadenomas, 17 serous cystadenomas, 9 pseudocysts, 5 solid pseudopapillary tumors, 2 carcinomas, 1 cystic pancreatic endocrine tumor, and 2 other cystic lesions. Seven mucinous cysts without neoplastic features were identified, representing 2 percent of all pancreatic resections, 7 percent of all resected cysts, and 10 percent of the 68 mucinous cysts. There was no evidence of cytologic atypia, papillary growth, or ovarian-type stroma in any of the cases. MUC1, MUC2, and MUC5AC were expressed in 83, 0, and 100 percent, respectively. There has been no recurrence with a mean follow-up of 44 months. This underappreciated entity belongs to the family of mucinous pancreatic cysts. However, unifying clinical characteristics that would prevent unnecessary resections in patients harboring these seemingly benign lesions are currently lacking [542].

NON-PANCREATIC PERIAMPULLARY CANCER

Duodenum

Cancer

Duodenal adenocarcinoma is a relatively rare malignancy and pancreaticoduodenectomy would be a standard procedure to achieve curative resection. It was reported a case of resection of the 2nd portion of the duodenum with nodal dissection preserving the pancreas. The patient was a 75-year-old man with right-sided paresis suffering from early cancer in the 2nd portion of the duodenum. Despite 3 times of endoscopic mucosal resections, mucosal local recurrence was found. The depth of the tumour involvement continued to be limited within the mucosal layer. It was performed segmental duodenal resection with nodal dissection sacrificing the minor papilla, while preserving the pancreas and the major papilla. The pathological diagnosis was primary intramucosal adenocarcinoma; the surgical margin was negative for cancer and there was no nodal metastasis. This procedure can be an alternative to pancreaticoduodenectomy in patients with earlystage adenocarcinoma in the 2nd portion of the duodenum when the major papilla can be spared, especially in high-risk patients [543].

GIST

Gastrointestinal stromal tumors (GISTS) are the most common mesenchymal tumors of the gastrointestinal tract. Type 1 neurofibromatosis (von Recklinghausen disease) is known to be associated with GIST. GISTs are rare mesenchymal tumors of the digestive tract. They commonly occur in persons 50 years of age or older, most commonly in the stomach (60 %), but they may also develop in the duodenum (4-5 %). They tend to present as solitary tumors and more rarely as multiple tumors in one or more organs. Multiple GISTs may be sporadic lesions or may occur in association with specific syndromes such as type 1 neurofibromatosis (NF1), which has an incidence that has been evaluated as being between 4 and 25 percent. NF1, or von Recklinghausen disease, is an autosomal dominant disorder that results in the mutation of the NF1 gene, leading to an increased risk for the development of tumors throughout the gastrointestinal tract. Cases of multiple duodenal GISTs in patients with known NF1 have been reported. Most sporadic GISTs express c-kit and PDGFRA (platelet-derived growth factor receptor alpha) gene mutations. Some authors have described an absence of C-kit or PDGFRA mutations in NF1-associated GISTs and suspect a pathogenesis that is different from that of sporadic GIST. In contrast, cases with the same immunohistochemistry as sporadic GIST have also been reported. It was now presented a 56-year-old man with no previous medical history who presented with epigastric pain and anemia. The clinical examination showed multiple subcutaneous nodes in the trunk. The upper gastrointestinal endoscopy revealed two submucosal tumors of 20 and 8 mm in the second part of the duodenum, which narrowed the lumen and was associated with 2 additional lesions of less than 1 cm in the third part of the duodenum. Endoscopic ultrasonography confirmed these multiple submucosal duodenal tumors without involvement of the mucosa. Multiple nonspecific lymph nodes surrounded the duodenum. At biopsy, fusiform cells, suggesting GIST, were found. The colonoscopy was unremarkable, as was the thoracoabdominal CT scan. Surgical management was chosen. At the laparotomy, multiple duodenal tumors were confirmed (with 2 lesions measuring more than 1 cm, close to the papilla), as well as 6 additional tumors measuring less than 3 mm in the jejunum. Pancreas-preserving duodenectomy and several wedge resections in the jejunum were performed. Reconstruction included a duodenoiejunal anastomosis immediately after the pylorus and a choledoco-wirsungo-jejunal anastomosis 15 cm farther down. The pathologic examination confirmed the multiple duodenal and jejunal GISTs and a low risk for recurrence, according to the Miettinen classification (<5 mitosis/50 hpf). Immunohistochemistry revealed C-kit- (CD117) and CD34- positive lesions. The biopsy of 1 of the subcutaneous nodes confirmed neurofibroma. The diagnosis of type 1 neurofibromatosis (von Recklinghausen disease) was confirmed by the genetic tests. The patient was discharged on postoperative day 20 and remained free of disease at 8 months of follow-up. The prognosis of GISTs is influenced by the completeness of the initial resection. Various surgical options are available to handle a duodenal GIST: partial duodenectomy, duodenectomy without pancreatectomy, or pancreaticoduodenectomy. The choice of surgical procedure for a duodenal GIST is guided by the size and the exact location of the tumor. Lymphadenectomy is not warranted in the case of a GIST; complete en bloc resection is enough. The risk for recurrence is not related to the type of resection, provided that it is complete and conservative strategies offer better functional outcomes [544].

Familial adenomatous polyposis

Pancreaticoduodenectomy is an alternative to pancreas-sparing duodenectomy for radical treatment of duodenal lesions. The aims of this study were to assess the results of pyloruspreserving pancreaticoduodenectomy (PPPD) for severe duodenal polyposis in familial adenomatous polyposis in terms of morbidity, long-term influence on functional results, the recurrence rate of cancer or jejunal polyps, and survival. All patients operated on for a PPPD between 1992 and 2009 were included. Clinical data, endoscopic findings, and pathologic examinations were evaluated. A total of 19 patients underwent PPPD for severe duodenal polyposis (17 Spigelman IV, 1 Spigelman III, and 1 invasive carcinoma). Postoperative mortality was nil. The postoperative morbidity rate was 42 percent, including 4 pancreatic fistulae (21 %) and 2 delayed gastric emptying (11 %). Pathologic examination found 7 invasive carcinomas, of which only 1 was known before resection. One third of patients operated on without a preoperative diagnosis of malignancy already had an invasive duodenal carcinoma. After a mean follow-up of 58 months, 16 patients were alive. Thirteen patients underwent endoscopic follow-up, and new adenomas were found in 4 (31 %). All were treated successfully during the same endoscopic procedure. PPPD did not modify the functional result after coloproctectomy. It was concluded that PPPD remains a safe and efficient therapeutic option for severe duodenal polyposis in familial adenomatous polyposis patients [545].

Endoluminal ultrasound of neoduodenum

Familial adenomatous polyposis affects around 2-10 per 100,000 population. Untreated, it inevitably leads to colon cancer. Prophylactic panproctocolectomy has led to improved survival. The resulting extension to follow-up has revealed that 70-100 percent of patients with familial adenomatous polyposis go on to develop duodenal polyposis and the lifetime risk of duodenal carcinoma in this group is up to 10 percent. Treatment for those not locally resectable requires pancreaticoduodenectomy. In recent years, pancreas-preserving total duodenectomy has emerged as a safe alternative to pancreaticoduodenectomy. Endoscopy has previously been safely performed in patients following pancreas-preserving total duodenectomy. It was reported successful endoscopic ultrasound (EUS) assessment and trans-neoduodenal EUS-guided fine needle aspiration biopsy (EUS-FNA) of the pancreas and adjacent tissue in a 45-year-old man with familial adenomatous polyposis who has previously undergone pancreas-preserving total duodenectomy. EUS confirmed the mass was most likely to represent a metastasis in a local lymph node. EUS-FNA confirmed invasive malignancy. A Kausch-Whipple pancreaticoduodenectomy was performed successfully and post-operative recovery has been excellent. The authors consider this to be the first report of successful EUS and EUS-FNA performed through the neoduodenum fashioned during pancreas-preserving total duodenectomy [546].

Endoluminal mucosal resection

Duodenal lesions (DLS) are common in patients with familial adenomatosis polyposis (FAP), and screening for duodenal adenocarcinoma (DA) is currently recommended. Endoscopic

treatment of DLS is controversial. The records of patients with FAP who underwent endoscopic surveillance or therapy for DLS over a 15-year period were reviewed. Endoscopic intervention included endoscopic surveillance with biopsies, argon plasma coagulation (APC), endoscopic mucosal resection (EMR), EMR with APC, and ampullectomy. Main outcome measurements were recurrence and histology of DLS after endoscopic therapy, complications of endoscopic therapy, and need for duodenectomy. Seventy-one patients with FAP and DLS were identified from an endoscopy database as undergoing upper endoscopy for screening and/or surveillance (1995-2009). Mean follow up was 5 years (1-15 years). Seventy of the seventy-one (99 %) patients had multiple flat DLS. Most of the patients were followed with yearly biopsies. APC was performed in 17 patients and EMR was performed in eight patients; in five of the eight EMR patients, APC was also performed to treat the edges of EMR site. During the follow up, 17/55 (31 %) patients had histological progression. This was also seen in 5/16 (31 %) patients who underwent APC (one was lost to follow-up) and 12/40 (30 %) patients followed with biopsies alone. Recurrence of lesions was noted in all patients. Two patients underwent duodenectomy. None of the patients developed DA during follow up. Endoscopic surveillance with directed endotherapy for DLS in FAP is feasible and safe when diligently performed [547].

Inflammatory myofibroblastic tumours (IMT)

Inflammatory myofibroblastic tumours (IMTs) of the duodenum and head of the pancreas are rare. They are of probable immunological aetiology and preoperatively indistinguishable from adenocarcinomas of the pancreatic head. It was described a patient with duodenal IMT and gastric outlet obstruction, and present a review of pancreatic head and duodenal IMTs in the literature. IMTs of the pancreatic head present as obstructive jaundice, while those of the duodenum present as gastric outlet obstruction. Surgery is the primary modality of treatment. Adjuvant chemotherapy and radiotherapy are controversial and reserved for incomplete resections and IMTs of a pathologically aggressive nature. Otherwise, recurrence is uncommon and surgery curative [548].

Papilla of Vater

Ampullary cancer is considered to have a better prognosis than cancers of the distal bile duct and pancreas, and recent publications emphasize the prognostic importance of the histologic differentiation of the intestinal and pancreatobiliary types of ampullary cancer. The aims of one study were to identify those factors that affect recurrence after curative resection and to investigate differences between the clinicopathologic features of these two pathologic subtypes. The medical records of patients that underwent pancreatoduodenectomy for ampullary carcinoma from 1995 to 2009 at one institute were retrospectively reviewed. One hundred and four patients that underwent curative resection for ampullary carcinoma were enrolled in this study. One pathologist reviewed all pathologic reports and histopathologic findings. Data on clinicopathologic factors and disease free and overall survival were analyzed. The 3- and 5-year disease free survival rates of the 104 study subjects were 62 percent and 58 percent, respectively, and overall survival rates were 69 and 60 percent, respectively. Multivariate analysis showed that an advanced T stage, the presence of lymph node metastasis, poor differentiation, and the pancreatobiliary type significantly increased the risk of recurrence. Furthermore, the pancreatobiliary type was found to be more associated with an advanced T stage, regional lymph node metastasis, and perineural invasion than the intestinal type. In addition, pathologic subtype analysis showed that Carcinoembryonic antigen (CEA) level and lymph node metastasis were important predictors of recurrence in patients with the intestinal and pancreatobiliary types, respectively. In conclusion, an advanced T stage, nodal metastasis, poor differentiation, and the pancreaticobiliary type were found to be independent predictors of recurrence after curative

resection of ampullary carcinoma by multivariate analysis. In addition, the pancreatobiliary type tended to present in a more advanced T stage and more frequently with regional lymph node involvement and perineural invasion than the intestinal type. Furthermore, CEA level and lymph node metastasis were found to be independent predictors of recurrence for the intestinal and pancreatobiliary types, respectively [549].

Pancreas-sparing duodenectomy (PSD)

Ampullary cancer has a different form of biology when compared with pancreatic cancer. Less invasive surgery should thus be considered for ampullary carcinoma without pancreatic and diffuse lymph node involvement. The role of pancreas-sparing duodenectomy (PSD) in the treatment of ampullary carcinoma with local lymph node metastasis remains controversial. In patients with a low-risk ampullary cancer in stages pTis N0 M0, the local resection with ampullectomy including local lymph node dissection seems to have a good long-term prognosis. Because PSD ensures resection of all layers of the duodenum and excision of the common channel outside of the duodenum, it enables wider tumor excision and less local recurrence compared to ampullectomy. Given the fact that 20-40 percent pT1 patients have regional lymph node metastases, regional lymph node dissection should be essential for ampullary cancer. Lymphadenectomy, however, has never been promoted as a regular procedure of PSD. The most common sites of lymph node involvement are the posterior/superior surface of the pancreatic head (87 %), SMA (33 %), and the common hepatic artery (13 %).Lymphadenectomy during PSD usually limited to the hepatoduodenal ligament (JPS LN12 and LN8) and the anterior/posterior pancreaticoduodenal surface (JPS LN6, LN13, and LN17), because it is very difficult to retrieve the lymph nodes along the SMA by using the standard approach without resection of pancreatic head The aim of one study was to investigate the feasibility, safety, and long-term prognosis of PSD with regional lymphadenectomy in the treatment of early-stage (pTis/pT1) ampullary carcinoma with or without regional lymph node metastasis. Between 2005 and 2009, 31 consecutive patients with ampullary carcinoma were enrolled in one study; 25 underwent PSD. A retrospective control group of 28 patients who underwent pancreatoduodenectomy (PD) for ampullary carcinoma during the same period was established. These 2 groups were matched in terms of demographic data, tumor size, and TNM classification. In the PSD group, 9 patients (36 %) had regional lymph node metastasis, and 23 patients (92 %) had R0 resection. Patients who underwent PSD achieved favorable results in intraoperative blood loss, duration of hospital stay, and morbidity rate. The 3-year overall and disease-free survival in PSD group were 72 and 61 percent, respectively. There were no differences in hospital mortality and longterm survival between the 2 groups, even for patients with lymph node metastasis (N1). It was concluded that PSD with regional lymphadenectomy is feasible and safe in the treatment of pTis/pT1 ampullary carcinoma with or without regional lymph node metastasis. Long-term survival and morbidity rates are also favorable. PSD can be performed as an alternative of PD in selected patients with ampullary carcinoma [550].

Annular pancreas

An annular pancreas is an uncommon congenital anomaly that usually presents early in childhood. Malignancy in the setting of an annular pancreas is unusual. It was reported a case of annular pancreas with carcinoma of the papilla of Vater. A 59-year-old man presented with epigastric discomfort and was referred to us after gastroduodenal endoscopy showed a tumor of the papilla of Vater. Preoperative imaging showed the pancreatic parenchyma encircling the descending duodenum and a tumor at the papilla of Vater. A pancreaticoduodenectomy was performed for the annular pancreas and the ampullary tumor. Histological examination confirmed a complete annular pancreas and carcinoma in situ of the papilla of Vater. It was also provided a review of the reported cases of an annular pancreas

with periampullary neoplasms and discussed the clinical characteristics of this anomaly [551].

Endoscopic ampullectomy

The utility of endoscopic ampullectomy versus surgical ampullectomy remains a topic of debate, particularly for the treatment of malignant tumors. The goal of this study was to prospectively establish the outcomes of endoscopic ampullectomy, with focus on carcinoma. From 2002 to 2008, 61 patients underwent endoscopic ampullectomy. The ampulloma was discovered fortuitously in the majority of cases (43 patients, 70 %). All patients had had an echoendoscopy revealing a T1N0 lesion without invasion of the orifice. Forty-three patients (70 %) underwent a monobloc resection. Histological analysis revealed a low-grade dysplastic adenoma in 21 patients (35 %), a high-grade dysplastic adenoma in 11 patients (18%), no dysplasia in 16 patients (26%), an adenocarcinoma in 10 patients (16%), and a well-differentiated endocrine carcinoma in 3 patients (5 %). Among the ten patients with adenocarcinoma, four with adenocarcinoma of poor prognosis were treated by pancreaticoduodenectomy (PD) with R0 resection, of whom one patient had no more lesion. Two intramucosal adenocarcinomas were cured by endoscopic ampullectomy without any recurrence. Four patients received palliative care after endoscopic ampullectomy due to cephalic pancreatico-duodenectomy contraindication. For the three patients with welldifferentiated endocrine carcinomas, one was treated by PD with R0 resection and two were treated solely by endoscopic ampullectomy, without recurrence. Eleven patients (18 %) presented with complications. The complication rate was 31 percent for carcinomas versus 15 percent for benign tumors. Endoscopic ampullectomy allows for the oncologic resection of well-differentiated intramucosal carcinomas with negative margins. The risk of complications is greater for papillary carcinomas [552].

Advances in endoscopic ampullectomy continue to mitigate concerns regarding incomplete removal of ampullary neoplasias, postprocedure complications, and insufficient treatment of tumors with undetected malignant foci or intraductal invasion. Advanced T staging of these lesions with endoscopic ultrasound and intraductal ultrasound, while useful tools for selection of candidates for snare polypectomy, should be limited to lesions either greater than 3 cm, bearing the macroscopic appearance of malignancy or unamenable to endoscopic therapy. Intraductal ultrasound has demonstrated T-staging accuracy superior to endoscopic ultrasound. One prospective study of prophylactic pancreatic stent placement and a number of retrospective studies have reported reduced complication rates. Recent studies continue to propose follow-up endoscopic retrograde cholangiopancreatography at 3-month intervals after ampullectomy to evaluate for recurrence and ablate residual tissue, with the interval increased to 6 to 12 months for 5 years on obtaining negative biopsies for adenomatous tissue. The development of thermal ablation, notably argon plasma coagulation, for fulguration of residual unresectable tumor, biductal sphincterotomy and prophylactic pancreatic pancreatic stent placement, and advanced diagnostic imaging mitigate the concerns leveled against endoscopic ampullectomy. In experienced hands, endoscopic papillectomy of noninvasive, benign ampullary lesions is a safe, technically feasible, and effective alternative to surgical resection. One study will focus on diagnosis and staging of ampullary adenomas and reviews indications for, and outcomes and complications of, endoscopic papillectomy [553].

Lower bile duct

Adenosquamous carcinoma of lower extrahepatic bile duct

It was reported a 83-year-old female with bile duct cancer who underwent subtotal stomach preserving pancreatoduodenectomy. Pathologically, her tumor was diagnosed as adenosquamous carcinoma of the lower extrahepatic bile duct with final stage IVb[pT3pN3M(-)].The prognosis of patients with adenosquamous carcinoma of the bile duct is very poor, and the reason is thought to be its tendency to invade the pancreas.Although she was an aged patient, we performed adjuvant chemotherapy using gemcitabine. No recurrence has occurred until this day, 30 months after the operation.This is thought to be an effect of the adjuvant chemotherapy, considering its poor prognosis [554].

OTHER RARE PANCREATIC TUMORS

Imaging features of the less common pancreatic masses

Contrast-enhanced multiphase CT and dynamic gadolinium-enhanced MR have been validated in the literature as outstanding modalities for the evaluation of pancreatic pathology. In addition to the more frequently seen pancreatic adenocarcinoma, neuroendocrine tumors of the pancreas and cystic lesions such as serous and mucinous cystadenomas and IPMNs, a variety of benign and malignant lesions may occur in the pancreas. The purpose of one pictorial essay was to review the imaging findings of a variety of uncommon, benign and malignant, pancreatic neoplasms [555].

Selected case materials

Advancement of imaging techniques and the improved awareness of clinical and pathological features of pancreatic neoplasms increasingly lead to the detection of rare solid intrapancreatic neoplasms that are difficult to differentiate from primary pancreatic ductal adenocarcinoma or neuroendocrine tumors. Rare solid tumors of the pancreas can be misinterpreted as primary pancreatic cancer. The aim of one study was to report our experience in the treatment of patients with rare tumor lesions of the pancreas and to discuss clinical and pathological characteristics in the context of the role of surgery. Data from patients of our prospective data-base with rare benign and malignant tumors of the pancreas, treated in our division from 2004 to 2010, were analyzed retrospectively. One-thousand and ninety-eight patients with solid tumors of the pancreas underwent pancreatic surgery. In 19 patients (10 women, 9 men) with a mean age of 57 years (range: 20-74 years) rare pancreatic tumors (metastasis, solid pseudopapillary tumor, teratoma, hemangioma, accessory spleen, lymphoepithelial cyst, hamartoma, sarcoidosis, yolk sac tumor) were the reason for surgical intervention. From 2004 to 2010 we operated 19 patients with rare pancreatic neoplasms. After extended preoperative diagnostics in the majority of patients (n=11) pancreatic cancer was suspected. Two of these patients presented with elevated tumor markers, two other patients with jaundice and three patients reported a positive family history of pancreatic carcinoma. At other medical institutions endoscopic ultrasound and fine needle biopsy were done in two patients and diagnostic laparoscopy was done in one patient without any histological evidence. Later on, intraoperative examination of frozen sections of the resected specimens and postoperative histological investigations excluded pancreatic cancer and detected in 10 patients the below described rare benign pancreatic tumors. In a 68-year-old male patient without any medical history of sarcoidosis, pancreatic sarcoidosis was the cause of a mass in the head of the pancreas accompanied by an elevation of the tumor marker CA 19-9 (199 U/mL; reference range: 0-37 U/mL). Pancreatic sarcoidosis is extremely uncommon. The first case was described on autopsy in 1937. Comparable to this case, the patients presented with all the signs and symptoms of a pancreatic malignancy, which was confirmed on a CT scan. The CA 19-9 level is also confirmatory of the suspected diagnosis. Comparable to this case, the disease most often presents as a pancreatic head mass. The preoperative diagnosis of this entity is a clinical challenge, and surgical intervention is usually needed to make a definitive diagnosis. In two male patients (57 and 58 years of age) an asymptomatic mass of 4 cm in the tail of the pancreas was identified as mature teratoma and distal pancreatectomy was performed. In one patient the tumor marker CA 19-9 was elevated (66 U/mL). Teratoma of the pancreas were first described in 1918 by Kerr. They can be classified as benign, well-differentiated lesions, which are solid or cystic, and solid malignant undifferentiated tumors, named, respectively, mature and immature teratomas. Surgical therapy is the only way of guaranteeing definitive resolution. Even though ultrasound, CT and MRI may be helpful, there are no pathognomonic data for their preoperative recognition. A 74-year-old male patient was hospitalized following painful

jaundice. MRI and CT showed a double duct sign and a mass of 8 cm diameter in the pancreatic head. Stenting of the common bile duct and diagnostic laparoscopy for taking biopsies was performed at another hospital before. As the mass was suspicious for carcinoma and biopsies did not confirm the diagnosis, surgical exploration was done at our department. A large tumorous mass was found in the pancreatic head and peritumorous inflammation involved vessels, stomach and the rest of the pancreas thus total pancreatectomy was carried out. Histological examination of the resected specimen revealed a benign lymphoepithelial cyst of the pancreas. Lymphoepithelial cyst is a rare benign lesion which was described for the first time in 1987 by Truong et al. Histologically, the lesion has a complex content consisting of keratinous material and a wall lined with mature squamous epithelium surrounded by dense lymphoid tissue. The most common symptoms are abdominal pain, nausea and vomiting, anorexia and weight loss, but many patients are asymptomatic, coming to the surgeon's attention as incidental radiological finding. Lymphoepithelial cyst may appear either multilocular (60 %) or unilocular (40 %) as described in this case. The etiopathogenesis as well as histogenesis of lymphoepithelial cyst remain unclear. They have been described in other locations which are associated with autoimmune diseases and states of immunological depression, frequently. Imaging may be not specific and the radiological appearance of these lesions differs. Surgical resection should still be considered the standard therapy, in suitable patients, to exclude malignancy. The prognosis is fairly good. There has never been a report of local recurrence after operative resection. Another 53-year-old male patient underwent extirpation of a 8 cm diameter asymptomatic hemangioma of the pancreatic head. Pancreatic hemangiomas are extremely uncommon benign pancreatic vascular neoplasms. In contrast to infantile hemangioma – that mostly presents before 6 months of age, grows rapidly, and then regresses spontaneously over several months - adult pancreatic hemangiomas do not regress and reveal a risk of bleeding. An intrapancreatic accessory spleen was found in a 67year-old male patient. A mass of 1.5 cm diameter in the pancreatic tail was detected in a routine check-up. Due to a family history of pancreatic cancer (mother and sister) surgical exploration and distal pancreatectomy were done. Autopsy studies suggest that in 80 percent the accessory spleen is located at or near the splenic hilum. The second most common site is the pancreatic tail. Most often an intrapancreatic accessory spleen is small with a diameter of less than 2 cm. Generally an intrapancreatic accessory spleen does not usually require treatment. Unfortunately, current CT, MRI, and ultrasound technologies do not necessarily distinguish between splenic tissue and pancreatic neuroendocrine neoplasms. Only nuclear medicine examinations/scintigraphy may confirm the diagnosis. Intrapancreatic accessory spleen is a rare cause of unnecessary laparotomy, but the absence of reliable diagnostics for this entity makes histologic ascertainment of a benign tumor indispensable. An asymptomatic mass of 5 cm diameter in the processus uncinatus of the pancreas, enlarged peritumoral lymph nodes and a hypodense liver structure (segment VII) suggested a malignant pancreatic tumor in a 67-year-old male patient. MRI showed a stenosis of the pancreatic duct and PET-CT did not show any significantly increased activity. Total pancreatectomy was performed due to a soft fatty pancreatic tissue. Histopathological examination confirmed the diagnosis of a pancreatic hamartoma. A hamartoma is a mass composed of an excess of differentiated cells or mixture of cell types that are normally present in the organ where the mass is found. It may be regarded as a malformation rather than a neoplasm. Nearly all hamartoma arise in the head of the pancreas and tend to affect mostly males. Surgical resection and histopathological examination are required to confirm the diagnosis. In three patients (a 20-year-old female, a 51-year-old female, and a 26-year-old male) a solid pseudopapillary tumor of the pancreas was diagnosed. Solid pseudopapillary tumor (Franz tumor) accounts for less than 1 percent of all pancreatic tumors. It is of low-grade malignancy but can cause extensive local. Only about 8 percent of all cases were reported in males. About 15 percent are known to present with metastasis or recurrence. The only feature associated with malignant disease is tumor size (8 vs 4 cm) at presentation. Oncologic outcomes in patients who undergo surgical resection are excellent. Surgery including enucleation is typically curative in patients with localized disease and possibly in patients with limited metastasis. No consensus exists on an effective systemic therapy or radiation. In contrast to the above described rare benign intrapancreatic neoplasms, in a 69-year-old female patient, who presented with a mass in the body of the pancreas suspicious for pancreatic cancer, a malignant yolk sac tumor with peritoneal carcinosis and local infiltration of the stomach was diagnosed following surgical exploration. Yolk sac tumor also known as endodermal sinus tumor and Teilum tumor, is one type of germ cell neoplasm. Of all the genital tumors, yolk sac tumors are relatively uncommon and, unlike our case, they are mostly discovered in infants and adolescents (median age: 19 years). Yolk sac tumor is considered to be a highly malignant tumor that primarily occurs in the testis or ovary . Ten to fifteen percent of these tumors may arise in a variety of midline extragonadal sites. Exceedingly rare sites such as liver, kidney, omentum, stomach, spinal cord and pancreas have been reported. The imaging findings were verified by the morphological observations of an encapsulated tumor with focal necrosis. However in our patient CT was without any pathologic findings. The tumor in the body of the pancreas with a diameter of 3 cm was only detected by endoscopic ultrasound. Since yolk sac tumor usually show high malignancy, the duration from the onset of symptoms to the admission is always short and, as in our patient, metastasis may already exist at the time of the patient's admission. Surgical excision with combined adjuvant chemotherapy, as it was performed in our patient, is the treatment of choice. However, the prognosis is poor if there is metastasis. Eight patients presented with metastatic tumors to the pancreas (3 renal cell carcinomas, 2 melanomas, 1 duodenal gastrinoma, 1 breast cancer, and 1 retroperitoneal liposarcoma). Metastatic tumors to the pancreas account for less than 2 percent of all pancreatic malignancies. As with primary pancreatic cancer, early signs and symptoms of isolated pancreatic metastases are often nonspecific and subtle. Patients without symptoms at the time of diagnosis (43 %) account for the largest group. Most patients with a pancreatic secondary tumor are not candidates for resection because they have widespread disease. In our collective in three patients (two patients with renal cell carcinoma and one patient with breast cancer) surgical exploration showed widespread disease and resection was not possible. For improvement of life quality in one of these patients a palliative double bypass was created. Comparable to our observations most pancreatic metastases are referable to renal cell carcinoma [50]. However, metastases from primary lung, breast, colon, skin (melanoma), and sarcoma tumors also involve the pancreas. It was concluded that if rare benign and malignant pancreatic tumors, intrapancreatic metastasis, as well as pancreatic malformations or other abnormalities, present themselves as solid masses of the pancreas, they constitute an important differential diagnosis to primary pancreatic neoplasia, e.g. pancreatic ductal adenocarcinoma. Clinical imaging techniques cannot always rule out malignancy, thus operative exploration often remains the treatment of choice to provide the correct diagnosis and initiate adequate surgical therapy [556].

Double pancreatic cancers

The goal of one study was to identify clinicoradiologic characteristics to distinguish metastatic cancer to the pancreas (MCP) from double primary pancreatic cancer (DPPC). From 2000 to 2011, we retrospectively identified MCP and DPPC patients among patients with histories of other primary malignancies. A total of 94 patients with histories of other primary malignancies were histologically confirmed to have pancreatic cancer. Among them, 34 patients had MCP and 60 patients had DPPC, which were ductal adenocarcinomas. The kidney was the most common primary cancer site that metastasized to the pancreas (12, 35 %). In the DPPC group, the stomach was the most common primary cancer site (11, 18 %). There were 21 patients (62 %) with metachronous pancreatic cancer in the MCP group and 29 (48 %) in the DPPC group. Among the metachronous pancreatic cancer patients, the disease-free interval was 88 months in the MCP group, and 50 months in the DPPC group. The number of the patients who showed elevated CA 19-9 levels was higher in the DPPC group than in the

MCP group (39 vs 9). Total bilirubin and fasting plasma glucose were also higher in the DPPC group. The numbers of patients who showed pancreatic duct dilatation and pancreatic atrophy on radiographs were meaningfully higher in the DPPC group than in the MCP group. On the other hand, the numbers of patients who showed well demarcated tumor margin, tumor necrosis, enhancement, and distant metastasis were significantly higher in the MCP group than in the DPPC group. It was evaluated differences in survival between the two groups. The median survival time in the MCP group (55 months) was significantly longer than that in the DPPC group (20 months). It was concluded that other than elevated levels of CA 19-9, total bilirubin and fasting glucose, radiologic findings were the most reliable factors for distinguishing the MCP from the DPPC [557].

Large duct type invasive adenocarcinoma

A morphological variant of pancreatic ductal adenocarcinoma forming large ductal elements, large duct type ductal adenocarcinoma, is documented and its clinicopathological features are studied. These tumors may have microcystic and papillary growth patterns that closely mimic the non-invasive cystic and papillary pancreatic tumors such as: intraductal papillarymucinous neoplasia, including the oncocytic variant, mucinous cystic neoplasms, and ducts involved by pancreatic intraepithelial neoplasia. In a review of 230 pancreatectomy specimens with ductal adenocarcinoma, 28 (8 %) cases of large duct type ductal adenocarcinomas were identified according to following criteria: more than 50 percent of the tumor sections available for examination contained infiltrative ducts with a diameter larger than 0.5 mm or had a macroscopically identifiable microcystic pattern. Overall characteristics of large duct type ductal adenocarcinomas were not too different than those of conventional ductal adenocarcinomas, except that there was a slight female predominance in the former (F/M=2.3). The mean age was 67 (vs 63 in conventional ductal adenocarcinomas), and occurrence in the tail was slightly more common (40 % vs 18 % in conventional ductal adenocarcinomas). Grossly, cysts measuring up to 1 cm was noted in 10 cases. Microscopically, large duct type adenocarcinomas were characterized by irregularly distributed large ducts with jagged edges, lined by columnar mucinous cells often having deceptively bland cytological features and variable degrees of papillomatosis. Stromal desmoplasia had a hypercellular quality (morphologically distinct from ovarian-like stroma) in four cases, and had a myxoid quality in others. KRAS oncogene mutation was identified in 9 out of 11 cases. Median, 1-year and 2-year survival rates were 16 months, 77 percent and 30 percent, respectively, as opposed to 12 months, 52 percent and 30 percent, respectively, in conventional ductal adenocarcinoma. In conclusion, it should be recognized that, some (8 %) pancreatic ductal adenocarcinomas exhibit a large duct pattern that may microscopically mimic non-invasive pancreatic tumors characterized by cystic and papillary patterns. They may be distinguished by the relatively smaller size of the cysts, irregularity of the duct contours, clustering of the ducts, presence of intraluminal neutrophils and granular debris, degree of cytological pleomorphism, and myxoid quality of the stroma. Clinical behavior appears to be slightly better than that of conventional ductal adenocarcinoma, which may be accounted by the well-differentiated nature of these tumors [558].

Acinar cell carcinoma

Evaluation of the imaging features of pathology-proven acinar cell carcinomas (ACCs) of the pancreas using computed tomography (CT). It was reviewed the CT features, clinical presentations, and clinical outcomes of 15 patients (9 men, 6 women, mean age 62.3) with pathology-proven pancreatic ACCs. An abdominal radiologist retrospectively evaluated each patient's initial imaging study with respect to the lesion's size, location, attenuation (Hounsfield units) on arterial and venous phase images, peripancreatic lymphadenopathy,

and distant metastases. Additional parameters studied included biliary and pancreatic ductal dilatation, intratumoral hemorrhage, calcification, the presence of cystic/necrotic components, and whether the tumor was intraparenchymal or exophytic. The ACCs in this series were evenly distributed between the head/uncinate and the tail, were predominantly exophytic (73 %), tended to be large (average size 5 cm), and were mostly hypodense to the surrounding pancreas on both the arterial and venous phase images. A sizeable proportion demonstrated a cystic or necrotic component (53 %) and/or an enhancing capsule (53 %). Of those lesions in the head or uncinate process, very few resulted in pancreatic (28 %) or biliary (14 %) ductal dilatation. None of the lesions in this series showed internal calcification or intratumoral hemorrhage. While a prospective diagnosis is difficult, ACCs have several features which can differentiate them from ductal adenocarcinoma, including their large size, lack of biliary or pancreatic ductal dilatation, exophytic nature, and the presence of an enhancing capsule [559].

Acinar cell carcinomas (ACCs) are rare tumours of the exocrine pancreas accounting for about 1-2 percent of all pancreatic neoplasms in adults. It is therefore difficult to come across a large number of ACC cases in a single medical institution, and only a few serial studies have been published. Since ACCs present a wide variety of morphological patterns, immunohistochemical analysis is useful. In one study, the authors established a novel monoclonal antibody 2P-1-2-1 by means of a subtractive immunisation method. Immunohistochemical staining was performed using 50 primary pancreatic tumors, including 7 ACCs, 7 neuroendocrine tumours (NETs), 5 solid-pseudopapillary neoplasms (SPNs), and 31 ductal carcinomas and organs other than the pancreas. Non-neoplastic acinar cells were stained diffusely, but epithelial cells of the pancreatic duct and the islets of Langerhans were not stained. In pancreatic tumours, all the seven ACCs were diffusely positive for the 2P-1-2-1 antibody. However, no positive staining was found in other pancreatic tumours including NETs, SPNs and ductal adenocarcinomas. The sensitivity and specificity of the 2P-1-2-1 antibody for ACCs were both 100 percent. In other organs studied, positive staining was observed only in the ectopic pancreas. It was thus shown that the 2P-1-2-1 antibody specifically stained the pancreatic acinar cells and tumours of acinar cell origin, such as ACCs. Although it remains unclear at this time to which proteins the monoclonal antibody 2P-1-2-1 is directed, it is suggested to be useful for the pathological diagnosis of ACCs and for the exclusion of other pancreatic tumours [560].

Pancreatic acinar cell carcinoma (ACC) has several unique characteristics, such as its progression pattern, spreading into the pancreatic duct and large blood vessels, and its secretion of pancreatic exocrine enzymes, which induces a paraneoplastic syndrome. A 79year-old Japanese man, with medical history of chronic renal failure, was referred to our institution for the examination of his abdominal pain and hyperglycemia. Plain computed tomography demonstrated a mass lesion, 4 cm in diameter, in the body of pancreas. Abdominal ultrasonogram demonstrated a bulky, hypoechoic mass extending into the splenic vein. Multiple hepatic nodules were detected on suspicion of metastasis. Positron emission tomography using 18F-fluorodeoxyglucoase revealed the tumor extended towards the pancreatic head through the main pancreatic duct. It was obtained the tumor tissues from the pancreatic body using endoscopic ultrasound-guided fine-needle aspiration biopsy. Pathological diagnosis, supported by immunohistochemistry, was that of an ACC. In the follow-up period, he complained of subcutaneous nodules and arthralgia on his lower legs. Serum and intra-articular lipase levels were elevated, 6,420 I/U and 594 I/U, respectively. Histology of the skin lesion at the knee joint showed necrotizing panniculitis with eosinophilic infiltration. The patient was treated with weekly gemcitabine, but succumbed to acute respiratory distress unexpectedly 2 months after the initial diagnosis [561].

A novel antibody

Acinar cell carcinomas (ACCs) are rare tumours of the exocrine pancreas accounting for about 1-2 percent of all pancreatic neoplasms in adults. It is therefore difficult to come across a large number of ACC cases in a single medical institution, and only a few serial studies have been published. Since ACCs present a wide variety of morphological patterns, immunohistochemical analysis is useful. In this study, the authors established a novel monoclonal antibody 2P-1-2-1 by means of a subtractive immunisation method. Immunohistochemical staining was performed using 50 primary pancreatic tumors, including 7 ACCs, 7 neuroendocrine tumours (NETs), 5 solid-pseudopapillary neoplasms (SPNs), and 31 ductal carcinomas and organs other than the pancreas. Non-neoplastic acinar cells were stained diffusely, but epithelial cells of the pancreatic duct and the islets of Langerhans were not stained. In pancreatic tumours, all the seven ACCs were diffusely positive for the 2P-1-2-1 antibody. However, no positive staining was found in other pancreatic tumours including NETs, SPNs and ductal adenocarcinomas. The sensitivity and specificity of the 2P-1-2-1 antibody for ACCs were both 100%. In other organs studied, positive staining was observed only in the ectopic pancreas. It was shown that the 2P-1-2-1 antibody specifically stained the pancreatic acinar cells and tumours of acinar cell origin, such as ACCs. Although it remains unclear at this time to which proteins the monoclonal antibody 2P-1-2-1 is directed, it is suggested to be useful for the pathological diagnosis of ACCs and for the exclusion of other pancreatic tumours [562].

Cytostatics

Acinar cell carcinoma of the pancreas is a rare malignancy, accounting for 1-2 percent of pancreatic exocrine malignancies. This rarity makes it difficult to standardize a protocol of treatment for acinar cell carcinoma. A 71-year-old male without any particular past history was referred with abdominal distention and mild liver dysfunction. Computed tomography (CT) revealed a cystic lesion with a diameter of 3.5 cm, which originated from the neck of pancreas and had solid nodules inside. Several nodules were demonstrated surrounding the cystic tumor. Laparotomy and histological study demonstrated peritoneal dissemination of acinar cell carcinoma. The patient was treated with S-1 monotherapy (80 mg/m² for four weeks with a two-week interval as one cycle). After one cycle of S-1 monotherapy, CT demonstrated remarkable shrinkage of the main tumor and disappearance of the nodules on the peritoneum. The patient underwent a radical distal pancreatectomy. The patient was then treated with 16 cycles of S-1 monotherapy after the radical pancreatectomy and remains without any recurrence of the disease two years later. It was concluded that nitially inoperable acinar cell carcinoma was treated by monotherapy using S-1, resulting in curative operation and two years disease free survival post operation. S-1 might be more effective on acinar cell carcinoma, rather than gemcitabine [563].

Primary retroperitoneal acinar cell cystadenoma

In one report, it was described a case of hitherto unreported primary retroperitoneal acinar cell cystadenoma that morphologically and immunophenotypically resembled pancreatic acinar cell cystadenoma. Pancreatic acinar cell cystadenoma is a very uncommon benign lesion characterized by acinar cell differentiation, the evidence of pancreatic exocrine enzyme production, and the absence of cellular atypia. One case occurred in a 55-year-old woman presenting a 10-cm multilocular cystic lesion in the retroperitoneum thought to be a mucinous cystic neoplasm. At laparotomy, the cystic mass, which showed no connection with any organ, was completely resected with a clinical diagnosis of cystic lymphangioma. The diagnosis of retroperitoneal acinar cell cystadenoma was based on the recognition of morphological acinar differentiation, the immunohistochemical demonstration of the acinar marker trypsin, and the absence of cellular atypia. These peculiar features can be used in the differential diagnosis with all the other cystic lesions of the retroperitoneum [564].

Of the stomach

Acinar cell carcinoma is an uncommon carcinoma of the exocrine pancreas. On very rare occasions it has been reported in ectopic sites, sometimes with, but usually without contiguous heterotopic pancreatic tissue. Whilst mixed and composite glandular tumours have also been described, pure pancreatic-type acinar cell carcinomas arising in the stomach are very rare [565].

Pancreatic acinar differentiation in gastric adenocarcinoma:

Although pancreatic acinar metaplasia in the gastric mucosa is well recognized in chronic gastritis, gastric carcinoma with acinar differentiation is very rare. It was encountered a case of gastric adenocarcinoma with prominent histologic and immunohistochemical features of pancreatic acinar differentiation in the absence of identifiable heterotopic pancreatic tissue. Distinct glandular and diffuse patterns of adenocarcinoma were also present, and there was focal mucin production. The tumor strongly expressed pancreatic exocrine enzymes trypsin and chymotrypsin, and focal neuroendocrine staining was also present. To investigate the prevalence of acinar differentiation in histologically typical gastric cancers, we performed immunohistochemical staining for trypsin and chymotrypsin on a tissue microarray containing 111 conventional gastric adenocarcinomas (60 intestinal, 28 mixed, 22 diffuse type, and 1 undifferentiated). No obvious morphologic evidence of acinar differentiation was identified in any of the 111 cases. Although some cases showed equivocal staining for at least 1 exocrine enzyme on the initial tissue microarray sections, pancreatic repeat immunohistochemical staining on representative whole-tissue sections failed to reproduce positive staining. Thus, acinar differentiation is rare in gastric adenocarcinomas, other than in histologically unusual cases such as the one we report, and in others from the literature, which are reviewed [566].

Adenosquamous carcinoma

Adenosquamous carcinoma of the pancreas is rare. The understanding of the disease and its prognosis comes mainly from small retrospective studies. Using the Surveillance, Epidemiology, and End Results (SEER) database (1988 to 2007), it was identified patients with adenosquamous carcinoma (n=415) or adenocarcinoma (n=45,693) of the pancreas. The demographics, tumor characteristics, resection status, and survival were compared between the groups. Compared with patients with adenocarcinoma, patients with adenosquamous carcinoma were more likely to have disease located in the pancreatic body and tail (45 % vs 54 %). While the stage distribution was similar between the two groups, adenosquamous carcinomas were more likely to be poorly differentiated (71 % vs 45 %). node positive (53 % vs 47 %), and larger (5.7 vs 4.3 cm). For locoregional disease, resection increased over time from 26 percent in 1988 to 56 percent in 2007. The overall 2-y survival was 11 percent in both groups. Following resection, patients with adenosquamous carcinoma had worse 2-y survival (29 % vs 36 %). Resection was the strongest independent predictor of survival for patients with locoregional pancreatic adenosquamous carcinoma (HR 2.35). This is the first population-based study to evaluate outcomes in adenosquamous carcinoma of the pancreas. Compared with pancreatic adenocarcinoma, adenosquamous carcinoma was more likely to occur in the pancreatic tail, be poorly differentiated, larger, and node positive. The long-term survival following surgical resection is significantly worse for adenosquamous cancers; however, patients with adenosquamous carcinoma can still benefit from surgical resection, which is the strongest predictor of survival [567].

Solid pseudopapillary neoplasms (SPN)

Solid pseudopapillary neoplasms (SPNs) are rare lesions which make up 1-2 percent of all pancreatic cystic neoplasms. They are almost exclusively found in young women with a median age of 30 years. On the basis of the largest review, tumors ranged in size from 0.5 to 35 cm with a mean diameter of 6 cm. They are equally distributed throughout the pancreas. Solid pseudopapillary neoplasms often start as solid tumors and undergo degeneration giving it a cystic appearance on radiologic imaging. On CT and MRI, the tumor is often well circumscribed, encapsulated, and heterogeneous with hemorrhagic and cystic degeneration. Solid pseudopapillary neoplasms are tumors with relatively low malignant potential, with a reported incidence of malignant transformation of 15 percent. Surgical resection of distant metastases is justified due to the excellent long-term prognosis in the presence of metastatic disease [517].

The pseudopapillary tumor of the pancreas (or Frantz's tumor) is a rare exocrine pancreatic tumor with a low degree of malignancy. It occurs more frequently among women between 20 and 40 years of age and in the Asian population. This tumor is rarer in the pediatric population. The symptoms are subtle, the most striking being pain and an abdominal mass. Pathologically, the tumor is usually well circumscribed with regions of necrosis, hemorrhage and cystic degeneration. A thick, fibrous capsule is often present. The low grade of malignancy of this tumor with a fibrous capsule led to perform a surgical resection. The localization and local invasion determine the surgical technique. Despite its potential for local infiltration and metastatic disease (up to 15% confined often to the liver), the prognosis is favorable after a surgical resection with correct margins. Long follow-up is necessary to detect a possible recurrence, even late [568].

Solid pseudopapillary neoplasms (SPNs) are rare tumours of the exocrine pancreas. Although they can develop metastasis, the prognosis is good. The aim of one study was to describe the characteristics of these tumours attended in our hospital. All cases of SPN in the database of a pathology department between 1991 and 2010 were included. Age, gender, symptoms, type of surgery, pathologic and immunohistochemical characteristics, and clinical evolution were analyzed. Six cases were identified; all of them were women with a median age of 28 years. One patient presented haemoperitoneum, 2 abdominal pain and 3 were diagnosed incidentally. The most frequent localization was the pancreatic tail (n=4) and the median size was 8 cm. Four tumours were benign and 2 carcinomas. One of them had liver and lymph node metastases. Ki-67 proliferation index was low (1-3 %). After a median follow-up of 34 months, all patients were alive and without evidence of relapse. It was concluded that SPNs occur in young women. In most cases surgical resection is curative. A low mitotic index confers a good prognosis and a long survival [569].

The purpose of one study was to determine if characteristic features on computed tomographic and (or) magnetic resonance imaging can differentiate benign and malignant solid pseudopapillary neoplasms (SPN). A total of 82 pathologically diagnosed SPN patients were included. CT and MRI were reviewed by 3 radiologists. Each tumor was analyzed through the clinical and imaging features. The highest occurrence of malignant SPN was observed in the group of patients (11-19 years old) followed by the group of patients (50-65 years old). When the tumor was located in the tail and the size was equal or larger than 6.0 cm, the positive and negative predictive value, sensitivity and specificity for a malignant SPN were 62, 100, 100, and 79 percent, respectively. Presence of complete encapsulation was more frequent in benign SPNs, but focal discontinuity in the malignant SPNs. Amorphous or scattered calcifications, all near-solid tumors and presence of upstream pancreatic ductal was found in the benign SPNs. A focal discontinuity of the capsule, large tumor size (>6.0cm) and a pancreatic tail location may suggest malignancy of SPN. In contrast, tumors with amorphous or scattered calcifications, and all near-solid tumors may be indicative of benignancy. Age (less than 20 or more than 50 years old) is a possible risk factor of SPN. In

comparison to other pancreatic neoplasms, such as ductal adenocarcinoma, a complete/incomplete pseudo-capsule, without upstream pancreatic duct dilatation and lymph nodes metastasis, and the presence of internal calcification and hemorrhage are more likely SPN [570].

Clear cell variant

A clear cell variant of solid-pseudopapillary tumor (SPT) of the pancreas was initially reported in 2006 as a tumor that arose in the pancreatic body and tail in young adults; to date, only 4 cases of this entity have been reported. Here, it was presented the case of a 58-year-old man with clear cell variant of SPT with distinctive clinicopathologic features. The tumor was well demarcated, was 2.6 cm in size and mostly composed of multivacuolated clear cells with solid growth, and exhibited the characteristic immunohistochemical positivity of β-catenin in the cytoplasm and nuclei of the neoplastic cells. In contrast to classical SPT with nuclear positivity, this case was negative for E-cadherin. Direct DNA sequencing of exon 3 of betacatenin gene demonstrated a single amino acid substitution (serine to phenylalanine) in codon 37, which is the phosphorylation site by GSK β and frequently found in classical SPT. Electron microscopy demonstrated enlarged mitochondria and endoplasmic reticulum. Despite the fact that previous cases of clear cell variant of SPT arose mainly in the pancreatic body and tail in female young adults (age, 26-32 years), this case suggested that it is possible for a clear cell variant of SPT to arise in the pancreatic head in a middle-aged man. Because the recognition of the clear cell variant of SPT is important for the appropriate diagnosis of primary pancreatic tumor, the present case with its distinctive characteristics may provide new information for a more profound understanding of the pancreatic SPT [571].

Two types

To explore the correlation between imaging features of solid-pseudopapillary tumor of pancreas (SPTP) and their pathological findings the imaging of 19 patients (female 15, male 4, median age 25 years) who underwent surgery for SPTP were anlyzed and divided into solid-predominance type, solid-cyst type and cyst-predominance type to compare with their pathological specimens. All patients had plain and enhanced CT examination and plain and enhanced MR examination. Two cases were of solid-predominance type (11 %), 13 cases solid-cyst type (68 %), and 4 cases of cyst-predominance type (21 %). Cysts were located in the surrounding area of solid-predominance type; solid and cysts were mixed in cyst-solid type whereas cyst-predominance type had thick-walled cystic tumors with nodules. Twelve cases (63 %) showed obvious signs of hemorrhage and 4 cases (21 %) had calcification on CT. All cases (100 %) which on MR can be seen signs of hemorrhage. Pathological findings demonstrate SPTP have two ingredients: solid and cystic. However, the two ingredients occupy different ratio in different types. Hemorrhage is seen in all of tumors [572].

Immunohistochemistry

To study the clinicopathologic and immunohistochemical features, biological behavior, diagnosis and treatment of solid pseudopapillary tumor of the pancreas (SPTP) a retrospective clinical and clinicopathologic analysis was made on 33 cases of SPTP admitted from 2001 to 2010. There were 7 male and 26 female patients, aging from 13 to 66 years with a mean of 34.3 years. The tumor was located in pancreatic head of 10 patients, in pancreatic neck of 5 patients, in pancreatic body and tail of 18 patients. Of the 33 patients treated with surgery, 8 underwent simple resection of pancreatic tumor, 6 underwent pancreaticoduodenectomy, 3 underwent tumor resection plus pancreaticojejunostomy, 1 underwent tumor resection plus pancreaticogastrostomy, 11 underwent distal pancreatectomy, 4 underwent distal pancreatectomy plus spleen resection (1 underwent mesohepatectomy for hepatic metastasis). Sixteen of the 33 operations were completed by

laparoscopy. Histologically, tumors were composed of papillary and microcystic solid structures, with uniformed population of cells. The pancreas and blood vessels invasion were identified in 3 cases, one of them was combined with liver metastasis, and they are male. Immunohistogically, the tumors were positive for α 1-antitypsin, α 1-antichymotrypsin, β -catenin, CD10, CD56 and vimentin (all cases), neuron-specific enolase (3 cases), synaptophysin (6 cases), chromogranin A (4 cases), progesterone receptor (28 cases), estrogen receptor (3 cases), S-100 (6 cases). Totally 33 cases were followed up with a median period of 49 months without tumor recurrence. It was concluded that SPTP is of low graded malignancy. It primarily affects young women. It may be located in any part of pancreas. Immunohistochemistry is very important for the diagnosis and differential diagnosis of SPTP. Surgical resection is recommended as the treatment of choice. Laparoscopic distal pancreatectomy or tumor resection is feasible and safe for some selected patients, and the prognosis is good [573].

Contrast-enhanced US

The aims of one study were to determine the features of solid pseudopapillary tumors of the pancreas on contrast-enhanced sonography and correlate them with pathologic findings. Five patients with solid pseudopapillary tumors of the pancreas underwent conventional sonographic, color Doppler flow imaging, and contrast-enhanced sonographic examinations. Time-intensity curves were used to calculate the contrast enhancement times, wash-out times, and enhancement patterns of the lesions. Three of the 5 patients also underwent contrast-enhanced computed tomography. All cases were confirmed by surgery and pathologic examination. The study included 3 women and 2 men. Tumor diameters ranged from 4.4 to 13.0 cm. Sonography revealed round well-defined encapsulated tumors. Two appeared as mixed cystic-solid and 3 as solid masses on conventional sonography. One mass had a macrocalcification. Some areas of blood flow were seen in 3 of the masses on color Doppler flow imaging. On contrast-enhanced sonography, the peripheral rims of the tumors showed isoenhancement during the early arterial phase, and the interiors of the masses showed heterogeneous enhancement consisting of regions of isoenhancement, hypoenhancement, and nonenhancement. Progressive wash-out of the contrast agent during venous phases revealed hypoenhancement compared with normal adjacent pancreatic parenchyma. Pathologic findings showed that each tumor was completely encapsulated and had varying degrees of internal hemorrhage and necrosis. It was concluded that solid pseudopapillary tumors of the pancreas have characteristic findings on contrast-enhanced sonography, including peripheral rim isoenhancement and internal heterogeneous enhancement with nonenhanced portions; these features may help differentiate solid pseudopapillary tumors from other pancreatic neoplasms [574].

Surgery

Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare neoplasm that accounts for about 1 to 2 percent of all pancreatic tumors. The aim of one study was to delineate the clinicopathological characteristics and surgical outcomes of solid pseudopapillary neoplasm of the pancreas. It was retrospectively reviewed the clinicopathological characteristics and surgical outcomes of 18 patients who underwent surgery for SPN of the pancreas between 2001 and 2010. The patient group was comprised of 14 females and four males and the median patient age at diagnosis was 32 years (range 10 to 68 years). Eleven of the 18 patients were symptomatic at the time of diagnosis. The type of surgery was selected according to the location and presentation of the tumor. The resection margins were negative in all patients. One patient had distant metastasis and recurrent mass node repetitively. She underwent seven operations for recurrence of SPN during the follow-up period of 218 months. Complete surgical excision is the treatment of choice for SPN of the pancreas and can give a good prognosis. Although sometimes patients have repetitive metastases or

recurrences, patients undergoing complete surgical excision of the tumor will have a good outcome [575].

Peritoneal carcinosis

Solid pseudopapillary neoplasm (SPN) is a rare malignant tumour accounting for 0.1 percent to 2.7 percent of all pancreatic neoplasms and affecting young women. Peritoneal carcinomatosis (PC) is even rarer, with only 11 reported cases. We describe a twelfth case occurring 13 years after the resection of an SPN which ruptured peroperatively. This 35-year-old woman had first undergone complete cytoreductive surgery (CCRS) alone and disease had relapsed within 8 months. Ultimately, further CCRS was combined with hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin and irinotecan. The patient is now alive and disease free 31 months after her last operation. In the literature, the surgical treatment of PC from an SPN has yielded disappointing results, with a 58% recurrence rate at intervals ranging from 1 to 19 years. As none of these patients developed distant metastases, indicating a strictly peritoneal disease, HIPEC might be a solution for preventing such recurrences [576].

Late recurrence

A solid pseudopapillary neoplasm (SPN) of the pancreas is generally regarded as a neoplasm of low malignant potential and there is rarely recurrence of the disease. A 12-yearold female underwent a pylorus preserving pancreaticoduodenectomy for a ruptured pancreatic SPN following a blunt abdominal trauma. The tumor showed no pathological features suggesting malignant potential. Follow-up imaging studies depicted small nodules adjacent to the superior mesenteric vein 7 years after surgery. A laparotomy was performed, and exploration revealed 3 nodules adjacent to the superior mesenteric vein 7 years after surgery. A laparotomy was performed, and exploration revealed 3 nodules adjacent to the superior mesenteric vein and 4 small nodules in the mesointestine. All of these lesions were extirpated, and were histologically confirmed to be nodal and peritoneal recurrence of SPN. This case indicates that SPN of the pancreas has a latent ability to recur, regardless of its benign pathological features, and peritoneal spread may be promoted by trauma. A close postoperative follow-up is thus mandatory in all patients with SPN even after a radical resection [577].

Small cell carcinoma

Small cell carcinomas (SCCs) is an aggressive tumor, which account for 18-20 percent of all primary lung cancers, but they are also described in the urinary bladder, prostate, salivary glands, pharynx, larynx, esophagus, stomach, pancreas, colon, rectum, skin, and cervix. Similar to SCC of the lung, SCC of the pancreas (SCCP) is a lethal disease and its prognosis is extremely poor. If untreated, it progresses rapidly with fatal course. SCCP is a rare neoplasm, with only a few cases reported in the literatures. Among all the primary pancreatic neoplasms, only 1 percent of the neoplasms are SCCP. Preoperatively, it is difficult to distinguish SCCP from pancreatic adenocarcinoma by imaging studies. However, some studies have indicated that imaging studies might be helpful in the differential diagnosis of SCCs of the pancreas. Although pulmonary SCC are frequently associated with paraendocrine syndromes; extrapulmonary SCC does not accompanied with identifiable paraneoplastic syndromes frequently. Only two have reported that SCCP had elevated hormones levels: one with adrenocorticotrophic hormone (ACTH) secretion and the other with paraneoplasic hypercalcemia. Neuron-specific enolase (NSE), which is found in neuroendocrine cells, is a good marker for the diagnosis of pulmonary SCC. Serum NSE concentrations correlated with the extent of the disease and response to treatment. In other reported cases, NSE was increased also in SCCP. Therefore NSE could be considered as a tumor marker and could be used for diagnosis or assessment of treatment effect in patients

with SCCP. It has also been reported that serum carcinoembryonic antigen (CEA) concentrations might also be used for assessment of treatment effect but not good for the differential diagnosis, because the presence of a high CEA concentration in patients with SCCP is variable and CEA is not specific for SCCP but also frequently increases in patient with pancreatic ductal adenocarcinoma. Pro-GRP is known to be more stable than GRP and is more sensitive and specific tumor marker than NSE in pulmonary SCC. In a review of all published cases of SCCP, 91 percent have metastasizes at the time of initial diagnosis. In one report, the most frequent sites of metastasis were the peripancreatic lymph nodes (62) %), the liver (38 %), the lungs (14 %), the bone marrow (14 %), the bone (10 %), the colon (10 %), and the adrenal gland (10 %); rarer sites included the spleen, gallbladder, kidney, skin and brain. As for the pulmonary SCC, the encouraging long remission rates could be achieved by chemotherapy and/or radiation. Surgery alone is generally unsuccessful in managing either pulmonary or extrapulmonary SCC. Because the combination of cisplatin/etoposide is most frequently prescribed in SCCP, this combination is also widely used in SCCP. It has been reported complete remission of refractory SCCP with cisplatin and etoposide. Initial chemotherapy with streptozotocin, 5-fluorouracil, and methotrexate, doxorubicin, cyclophosphamide, and lomustine (MACC) had been unsuccessful. They used a schedule consisting of etoposide and cisplatin which made the patient remain in. It was presented a case of a 62-year-old man with a half-month history of upper abdominal discomfort who was diagnosed with SCC of the pancreatic tail. A Chest X-ray showed no evidence of primary lung tumor. The diagnosis of a SCCP was confirmed by post-surgery pathology and immunohistology. In our review of the published reports of SCCP, we only found a few cases reported in the literatures. The diagnosis of SCCP needs the post-surgery pathology and immunohistology and the prognosis of SCCP is extremely poor. There was a significant increase in median survival, from 1 to 6 months, in treated patients compared to patients treated only by symptomatic management. Chemotherapy was the most common treatment and the combination of cisplatin/etoposide was most frequently prescribed. The accurate diagnosis of SCCP is necessary for determining prognosis and deciding appropriate therapy [578].

Colloid carcinoma

Colloid carcinoma is considered a distinct type of pancreatic neoplasia with specific histopathological and molecular features, and a better prognosis. It was presented a case of a patient with a 15 cm locally invasive colloid carcinoma of the pancreas, in which an aggressive surgical approach achieved no evidence of disease 24 months after surgery. If an accurate diagnostic approach and surgical resection are performed, the 5-year survival rate can reach 60 percent. Presence of invasive intraductal papillary mucinous neoplasm has been reported, and this can affect the prognosis. Adjuvant therapy has not demonstrated improvement of survival in surgically-resected patients [579].

Choriocarcinoma

Pancreatic cancers can present with pancreatitis or its complications. Choriocarcinoma involving pancreas is a rare disease. Only few case reports available so far. Primary choriocarcinoma (extragonadal non gestational) is still rarer. A 27-year-old married woman presented to our facility with abdominal pain and fullness of 20-day duration. She was clinically diagnosed as acute pancreatitis with pseudocyst as a complication. Serum amylase was elevated with CT scan of abdomen showing a cystic lesion involving the pancreas. It was approached the cyst with endoscopic ultrasonography and cyst fluid was aspirated and analyzed. Cyst fluid amylase was elevated and cytology revealed germ cell tumor. Serum beta human chorionic gonadotropin was elevated. She had a swelling over the jaw which
also revealed choriocarcinoma in histopathological examination. Interestingly, this patient had tumor involving the left jaw as well which might be due to metastasis as histopathology showed the same type of cells. They present with elevated serum beta human chorionic gonadotropin and normal serum alpha-fetoprotein which differentiates it from other germ cell tumors affecting gonads. Choriocarcinoma is an aggressive malignancy with high metastatic potential. It responds well to chemotherapy [580].

Intraductal tubulopapillary neoplasm

Recently, a surgically resected case of intraductal tubulopapillary neoplasm (ITPN) with stromal osseous and cartilaginous metaplasia was encountered. A CT scan showed calcification at the tail of the pancreas two years before the operation. In the resected specimen, macroscopically, the main pancreatic duct was dilated and filled with a whitish solid mass without mucinous material. The tumor showed mainly a solid and papillary growth pattern. The tumor cells had no evidence of acinar differentiation. The tumor cells, at the tail of the pancreas, invaded focally to surrounding pancreatic parenchyma with stromal desmoplastic and fibrosclerotic reaction and also formed nodular stromal osseous and cartilaginous metaplasia. The tumor did not invade extrapancreatic tissue and showed no lymph node metastasis. As there were no signs of chronic calcifying pancreatitis, it is hypothesized that the metaplastic stroma was formed by a stromal reaction due to the tumor growth. It is thought, therefore, that the intraducal component of the tumor had existed at least for two years. This case suggests that ITPN is a relatively indolent tumor with a better prognosis than that of other types of invasive ductal adenocarcinoma of the pancreas [581].

Hepatoid cancer

Hepatoid carcinoma is a rare histopathological tumor type with prominent features of hepatoid differentiation, and while most of the reported cases are of gastric origin, ten cases of pancreatic hepatoid carcinoma have been reported to date. The majority of hepatoid carcinoma cases are metastatic at presentation, mainly to the liver, lymph nodes, and lungs. They are aggressive, invading, and proliferating in the venous and lymphatic systems, with a behavior similar to that of hepatocellular carcinoma. Diagnosis is challenging: alpha-Fetoprotein, the most useful marker, is not always positive. It was presented the first case of metastatic pancreatic hepatoid carcinoma treated with sorafenib, an oral multikinase inhibitor approved for advanced hepatocellular carcinoma that has antiangiogenic, pro-apoptotic, and raf-kinase inhibitory properties. The patient, a 37-year-old male, was diagnosed with hepatoid carcinoma of the pancreas that had metastasized to liver, lungs, and lymph nodes. The cytokeratin (CK) profile was useful for the diagnosis: Both the hepatoid and adenocarcinoma components of the tumors were CK18+, CK19+, and CK20+/-, whereas normal and neoplastic hepatocytes are CK18+, CK19-, and CK20-. Amylase, lipase, and liver enzyme levels were elevated, but bilirubin was normal. Treatment with sorafenib resulted in more than 7 months of progression-free survival. Therapy was discontinued after 8 months when his bilirubin level increased dramatically. Signs of liver failure resolved temporarily with insertion of a biliary stent, but his condition deteriorated and he died 3 months later, 1 year after diagnosis. In the absence of evidence-based experience with this rare and aggressive tumor and given its similarities with hepatocellular carcinoma, sorafenib should be considered as a possible treatment [582].

Hematological malignancies involving pancreas

Hematologic malignancies often involve the pancreas, causing potential diagnostic pitfalls and, rarely, potentially avoidable surgical resection. It was reviewed the spectrum of hematologic malignancies involving the pancreas and describe features useful in preoperative distinction from adenocarcinoma. Archived clinical, pathologic, and radiologic data (1965 to present) for hematologic malignancies involving the pancreas were reviewed and compared with the data for 157 surgically resected pancreatic adenocarcinomas. Of 42 cases, 27 (64 %) were clinically "suspicious" for hematologic malignancies. Of the remaining 15 cases, 4 patients underwent resection for presumed pancreatic adenocarcinoma. Isolated pancreatic masses proved most difficult to identify clinically. Significant factors in distinguishing hematologic malignancies from adenocarcinoma included history of hematologic malignancy, young age, large tumor size, low CA19-9 level, B symptoms, and lack of jaundice or diabetes mellitus. Various hematologic malignancies involve the pancreas, most commonly diffuse large B-cell lymphoma. Pancreatic masses are usually correctly identified clinically. Preoperative and operative sampling is strongly recommended when hematologic malignancies cannot be excluded [583].

Granulocytic sarcoma (choloroma)

Granulocytic sarcoma (GS) is an extramedullary solid tumor mass composed of immature myeloid cells. GS is a rare manifestation of acute myeloid leukemia (AML) usually arising during or after the course of the disease, in up to 8 percent of patients in autopsy studies. Occasionally, it can be the first and the only manifestation of AML, leading to diagnostic challenges. It was reported two exceptional cases of isolated pancreatic GS to focus physicians' attention to specific diagnostic and therapeutic strategies for a solid pancreatic mass. GS, also called chloroma, refers to the infrequent green color observed as a result of myeloperoxydase action in neoplastic cells. GS usually occurs simultaneously or follows the onset of AML in 3-10 percent of patients. Rarely, GS is the first manifestation of AML. GS may also be the first sign of transformation into AML in patients with myeloproliferative disorders or myelodysplasic syndrome. Other common sites of origin are soft tissues, lymph nodes, skin and bones, with abdominal origin being very rare. Even if GS incidence is increasing due to prolonged leukemic remission of AML, pancreatic GS cases have rarely been reported in the literature. Only 10 cases have been published, only four of which, in addition to the two reported in the present paper, were isolated pancreatic GS without bone marrow involvement. GS can occur in patients of all ages with a focus on male patients (male:female ratio 1.2:1) during the last decades of life (median age is 56 years, range: 1 month to 89 years). Even if the overall prognosis of AML is favorable, the association with GS makes worsens the prognosis because only 24 percent of patients with GS will be alive 2 vears after the initial diagnosis, with an overall median survival of 7 to 20 months. These observations show that clinicians should think about pancreatic GS when the pancreatic mass develops during or after AML. However, in the cases reported here in which GS was the first and the only manifestation of AML, diagnosis is challenging. Because surgery is not required and may probably worsen the prognosis due to the delayed administration of induction chemotherapy, all efforts should be made to obtain pretherapeutic biopsies for a pancreatic mass, especially if all of the biological and morphological exam results are not typical and in agreement. A positive diagnosis of GS is sometimes challenging and requires expert pathologists. Histological observation reveals myeloblats, promyelocytes and sometimes neutrophils. The definitive diagnosis of GS requires positive immunostaining for at least one of the myeloid-associated antigens (in decreasing frequency: CD68, MPO, CD43, CD45, CD117, CD99, CD33, CD34, CD13) associated with negative immunostaining for the lymphoid lineages (CD3 for T-cells and CD20 for B-cells). Major differential diagnoses are Hodgkin lymphoma, Burkitt lymphoma, large-cell lymphoma, and small round cell tumours. When a histological diagnosis of GS is made, bone marrow sampling is mandatory

to assess the absence of AML. The risk of metachronous AML occurrence in non-leukemic patients with GS is very high, with a median delay of 5 months; most patients will develop AML within 1 year. Therefore, early intensive (induction/intensification) chemotherapy similar to that used to treat AML should be administered, even in GS patients who did not present AML upon initial diagnosis. It was reported two clinical cases of primary granulocytic sarcoma of the pancreas that were diagnosed on the surgical specimen [584].

Extramudullary plasmocytoma

An extramedullary plasmacytoma is a discrete collection of monoclonal plasmocytes arising in tissues other than the bone. Gastrointestinal involvement has been reported in approximately 10 percent of cases and usually involves the liver; however, there have been a number of cases involving the pancreas. Although helical CT can be used to diagnose pancreatic plasmacytomas based on a typical radiological appearance, there are a number of pitfalls with CT including similar radiologic appearances of other pancreatic tumors, malignant seeding induced by CT biopsy, and creation of multiple secondary plasmacytomas precipitated by CT biopsy. Tissue diagnosis is critical to management in pancreatic lesions as the decision to pursue surgery (pancreatic adenocarcinoma) versus chemotherapy (lymphoma) or radiation (extramedullary plasmacytoma) is dependent on a correct tissue diagnosis. Tissue diagnosis can change morbidity and mortality with respect to specific treatment of pancreatic lesions in the milieu of pancreatic tumor variance. In the confirmed tissue diagnosis of pancreatic plasmacytoma, radiation and chemotherapy can be preferentially chosen over high risk surgery. EUS-FNA has a lower risk of malignant seeding, complications, and a high sensitivity in the diagnosis of pancreatic plasmacytomas, especially with an increased number of passes and bedside cytopathologists. It is concluded that it is important for physicians to have a high index of suspicion for diagnosing pancreatic plasmacytomas in the appropriate clinical setting (i.e. a previously diagnosed multiple myeloma, extramedullary plasmacytoma or any other plasma cell neoplasm). EUS-FNA is now an indispensable imaging modality to achieve the diagnosis of pancreatic extramedullary plasmacytomas with an inherently lower rate of complications, and should be the first choice for tissue evaluation [585].

Extramedullary plasmacytomas are plasma cell neoplasms in organs other than the bone marrow. Most are found in the upper respiratory tract. Involvement of the pancreas is rare. It was reported a case of pancreatic plasmacytoma in association with advanced multiple myeloma. Biopsy confirmed multiple myeloma. She then completed a second course of radiation and chemotherapy. Follow-up CT of the abdomen and pelvis showed significant reduction in the size of the pancreatic mass. Five percent of all plasma cell neoplasms involve organs outside the bone marrow. These tumors are called extramedullary plasmacytomas. They are usually diagnosed after multiple myeloma of the bone marrow. Although the majority of extramedullary plasmacytomas involve the upper respiratory tract, ten percent occur in the gastrointestinal tract, primarily the liver, spleen, or stomach. There are approximately 25 case reports of pancreatic involvement in the English language literature. While they can develop in any part of the pancreas, many of these lesions are located in the pancreatic head. Diffuse enlargement of the pancreas has also been reported. Patients will typically present with abdominal pain and obstructive jaundice from compression of the common bile duct. On CT, pancreatic plasmacytoma is commonly characterized as a homogeneously enhancing solid mass. While this appearance is unlike that of a pancreatic adenocarcinoma, it can be difficult to distinguish from hypervascular neuroendocrine tumors. Percutaneous or open biopsy as well as endoscopic ultrasound-guided fine needle aspiration can be helpful in ruling out the other differential possibilities for a pancreatic mass including serous and mucinous tumors [586].

Pancreatic involvement by plasma cell neoplasms is an extremely rare event, with only 50 cases described in the literature. They can present as a primary solitary extramedullary

plasmacytoma or plasmacytoma secondary to a plasma cell myeloma. Clinical manifestations are due to the presence of a pancreatic mass usually in the pancreas head, which causes extra-biliary obstruction and abdominal pain. Abdominal imaging including CT scan or endoscopic ultrasound with fine-needle aspiration tissue sampling is essential for the initial diagnostic procedure. However, immunohistochemical analysis of the biopsy specimen or flow cytometry of the aspirated material is crucial to prove the monoclonality and the final diagnosis of a plasma cell neoplasm. Management of these situations include radiotherapy, chemotherapy, surgery or combined therapy. Novel medications including the immunomodulatory drugs or the proteasome inhibitors followed by consolidation with intensive chemotherapy and haematopoietic stem cell transplantation are nowadays used as upfront treatment in the cases associated to a plasma cell myeloma [587].

PEComa

PEComas (perivascular epithelioid cell tumors) represent a group of mesenchymal neoplasms showing characteristic morphologic, immunohistochemical, ultrastructural, and genetic features. These neoplasms are usually considered benign, being often well circumscribed by a thin capsule and showing scarce atypia. However, in some cases, they show local invasion and multiple metastases and cause the patient's death. PEComas have been found in many locations, but only 7 cases have been described in the pancreas to date. Here, the authors report an additional case of this rare neoplasm and demonstrate the HMB-45 immunoreactivity of melanosomes or premelanosomes at the ultrastructural level [588].

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease characterized by proliferation of morphologically distinguishable smooth muscle cells in the lymphatics and lymph nodes of the pulmonary parenchyma in most cases. Extrapulmonary LAM is a rare condition and is found to occur concurrently, before or after pulmonary LAM, and show strong association with tuberous sclerosis. The literature regarding extrapulmonary LAM without associated pulmonary LAM is limited due to the extreme rarity of the cases. We hereby describe clinical, pathological and radiological features of primary pancreatic LAM presenting clinic-radiologically as pseudocyst of pancreas in a 43-year-old lady. The present case is unique as LAM in pancreas without associated pulmonary LAM has never been reported in the literature before [589].

Lymphoid hyperplasia

Reactive lymphoid hyperplasia (RLH) is a rare non-neoplastic extranodal pathology with exceedingly rare occurrence in the liver and pancreas. It was presented two cases of hepatic RLH, one which had coinciding pancreatic involvement. To the best of our knowledge, concomitant hepatic and pancreatic RLH has not been previously reported. It was also present a comprehensive review of the literature on hepatic and pancreatic RLH. An extensive literature search for all published reports on hepatic or pancreatic RLH was conducted. Data on clinical, radiographic and histopathological features were extracted in addition to therapeutic options and outcomes. Forty-two hepatic cases was 58 years, with a male-to-female ratio of above 1:7. Almost 25 percent of cases were associated with internal malignancy. Four hepatic cases were managed through active observation. The remainder (84%) underwent surgical resection. Due to their small number, no meaningful analysis could be made on the pancreatic cases. No recurrences were identified in any of the reported

cases. It was concluded that RLH should be considered in the diagnosis of hepatic nodules where biopsies fail to demonstrate malignant cells. Confirmed RLH lesions should be managed by active observation. Investigation and treatment of any potential source of lymphoid reactivity should be undertaken. More reports on pancreatic RLH need to be studied prior to drawing any useful recommendations on its management [590].

Castleman's disease

Historically this disease was first reported by Benjamin Castleman in a patient with a mediastinal mass, at first diagnosed as timoma. Posteriorly Castleman et al. published a series of another ten cases, describing clinical and histological aspects of this peculiar disease, calling attention to the lack of specific signs or symptoms that could at least suggest the disease. In 1969, Flendrig and Schillings while analyzing histological features of a series of patients, described another form of the disease, with systemic symptoms and polyadenophaty, different from the first report, called type I and II, respectively. In 1972 it was reported the histological variations hyaline vascular and plasma cellular and in 1978 the multicentric form along with clinical features and a poorer outcome of these patients, clearly different and some times the opposite of the unicentric form of the disease. The etiology and consequently the physiopathology of Castleman's disease is not clearly known and actually most theories point to different etiological factors depending in the form of presentation of the disease, either the localized, unicentric or the multicentric form. Moreover, the most valid hypothesis is related abnormal response to antigenic stimulation from viral origin, cursing with cell development disarrangements and lymph node enlargement similar to the one that occurs with hamartomas, chronic inflammatory processes, and also immunodepressive states such as HIV or HCV/HBV infections. More recently, interleukin 6 (IL-6) has been implicated in the pathogenesis of the disease. Among possible etiological agents found on literature are Epstein-Barr virus, toxoplasma and mycobacterium. Due to the rapid deteriorating condition of the patient we could not identify other diseases that could justify such an acute and systemic compromise of the patient, nevertheless immunohistochemical findings collected from the patient ganglia on necropsy came positive for Epstein-Barr. Treatment and prognosis of this disease will depend on the form presented. Although there are no randomized studies, most published series agree that surgical resection is the best therapeutic option for the localized, unicentric form of Castleman's disease, with favorable long term prognosis reports and no cases of malignant transformation. The occurrence of this form of the disease seems to be more common in young adults regardless of gender. Multicentric form of the disease still rises controversy and it is not well established the best treatment, due to poor prognosis and low rate of survival showing no, or very low, response to chemotherapy and radiation. This generalized form has higher incidence in the elder, masculine patients and, due to clinical and histopathological characteristics can be considered malignant disease. Castleman's disease or angiofollicular lymph node hyperplasia localized in the pancreas region is a rare clinical situation and most often verv difficult to diagnose and to exclude pancreatic malignancies as well. After the initial report of one patient from 1982 (firstly diagnosed with a pancreas tumor), there have been some reports of isolated cases in the literature were Castleman's disease located in the pancreas was only confirmed after pathologic study of the surgical specimen. In 2007 it was performed a retrospective analysis of eight cases of pancreatic localized Castleman's disease and reported the supposedly first case of Castleman's disease in the pancreas head Almost all patients have poor clinical conditions without any specific signs or symptoms. Although there are no comparative studies about the best treatment options, in all series that showed pancreatic lesions the surgical resection was carried on, probably due to diagnosis uncertainty in the preoperatively stage. However, certain imaging details, such as the macroscopic aspect and delimitation of the mass, as well as points of cleavage with the pancreas should be helpful to define and differentiate the Castleman's disease from

pancreas malignancies. Other diagnostic tools, like endoscopic ultrasound with guided biopsy, could be useful in establishing the Castleman's disease diagnosis before surgery. Evidence based data is insufficient to define the role of other options of treatment like chemo- and radio-therapy, although it has been reported the use of radiation for local unresectable disease. There are two basic types, the localized or unicentric form that might have vascular hyaline or a plasma cellular presentation, and the multicentric form; a more aggressive form that sometimes curses with neuropathy. Many denominations have been used in previous publications for this condition; such as: follicular lymphoreticuloma, lymph node hamartoma, linfoid angiohamartoma, giant lymph hyperplasia and benign giant lymphoma. However, the most used term is still Castleman's disease. The main site of unicentric or localized form is the thorax, specifically in the mediastinum. Castleman's disease localized in the pancreas topographic area that mimics a pancreatic neoplasm is an even more uncommon event, with available published data of less than 15 cases until now. It was presented a 64-year-old male patient with a six-month past history of asthenia, adynamia, and lack of general clinical conditions. Imaging studies showed a nodular hypoechoic mass in the pancreatic head. Enucleation of the lesion was performed. Histopathological study revealed unicentric form of Castleman's Disease. It was concluded that Castleman's disease mimetizing pancreatic tumor is uncommon and it also curses with a difficult preoperative diagnosis. Surgery seems to be the best therapeutic alternative for this disease [591].

Teratoma

Teratomas are neoplasms of germ cell origin that are able to generate tissues from the three germinal layers: endoderm, mesoderm and ectoderm. They can be classified as mature or immature on the basis of the presence of immature neuroectodermal elements within the tumor. The mature types can be further classified as solid or cystic. Mature cystic teratomas (also called dermoid cysts) are congenital well-differentiated cystic lesions, thought to arise from the inclusion of skin at the embryonic time of neural groove closure. They are typically located in the ovaries, but they may also occur in the pathway of ectodermal cell migration along the midline of the body, such as testes, cranium, brain, mediastinum, omentum, retroperitoneum, sacrococcygeal region, neck and abdominal viscera. The rarest site of presentation is the pancreas. In 2012 the world literature reports 33 cases of pancreatic mature cystic teratomas with complete data. The first case was described in 1918 by Kerr and it was not until the case published by Judd in 1922 that dermoid cysts were included in the classification of pancreatic cystic lesions by Primrose. The clinical presentation of mature cystic teratomas is not specific. Most of patients complained abdominal pain and presented a palpable mass in the upper abdominal quadrants. Only 6 cases of 33 (18 %) were asymptomatic. The median age at diagnosis was 40 years (range 0.3-74 years), without gender preference (15 females, 18 males). The location of mature cystic teratoma was the pancreatic head in 13 patients (39 %), the body in 12 (36 %), the tail in 5 (15 %) and unknown in 3 patients (9%). The median dimension of the lesion was 8 cm, ranging from 2 to 20 cm. From the analysis of the reported radiological findings, the appearance of these lesions depends on the proportions of the various tissues of which they are composed. The lesion would appear hyperechoic at US, with distinct margins and presence of calcified tissues (while in our case it was hypoechoic, without calcifications). At CT and MRI techniques, the characteristics suggesting the diagnosis of dermoid cyst are clear boundary of the uni- or multi-locular cystic mass, with solid components in varying proportions and areas of fat-like density or gross calcifications within the solid components. At histological examination, dermoid cysts present a wall composed of stratified squamous epithelium and underlying connective tissue. The cyst cavity contains a combination of both cystic and solid elements, including hair, teeth, calcium, cartilage, and dermal appendages such as hair follicles, sweat glands, and sebaceous material. Dermoid cysts are benign neoplasms,

although a small percentage of mature teratomas may develop into malignant forms: therefore, a complete sampling of the lesion is necessary to exclude the presence of immature foci. Up to now all pancreatic teratomas reported correspond to mature type, whose behavior is benign. Differential diagnosis and management of cystic lesions of the pancreas is challenging, mainly because of the hard distinction between the more common benign cystic lesions from their malignant counterparts. Among this wide spectrum of pathologies, it is imperative to rule out alarming lesions such as mucinous cystic neoplasms or IPMNs that are associated with a high risk of malignant degeneration that has been estimated to be 10-50 percent for mucinous cystic neoplasms and 35-45 percent for IPMNs. Preoperative EUS-guided FNA, with cytological, biochemical and tumor markers cyst fluid analysis seems to be a safe procedure to investigate pancreatic cystic lesions, but it does not allow an unquestionable diagnosis of nature and malignancy of the lesions. The cyst fluid analysis of the most common pancreatic cystic lesions reveals different patterns for the above mentioned parameters. The cytological examination of the fluid shows mucine-positive columnar cells with variable atypia in mucinous cystic neoplasms and IPMNs; cuboidal glycogen-rich cells can be found in serous cystadenoma, while macrophages and inflammatory cells can be seen in pseudocysts. Amylase dosage in the cyst fluid reveals very high levels (usually in the thousands) in pseudocysts, while low levels (<250 ng/mL) are found in serous and mucinous cystic neoplasms. High amylase levels would be consistently found in IPMNs, in contrast to mucinous cystic neoplasms, because of the connectivity to the pancreatic ductal system. Among the several cancer antigens that can be evaluated in the cyst fluid, CEA has been shown to be the most accurate to distinguish mucinous from nonmucinous cysts. High concentrations of CEA (>192 ng/mL) within cyst fluid are typical of IPMNs and mucinous cystic neoplasms, while serous cystadenoma and pseudocysts are usually associated with very low levels (<5 ng/mL) of this tumor marker. However, considerable overlap exists in cyst fluid CEA concentrations among these pancreatic cystic lesions and, moreover, CEA levels do not allow to distinguish benign from malignant mucinous neoplasms. Considering that radiological findings are often inconclusive, the ongoing diagnostic issue is to differentiate these lesions in a preoperative setting. In this context, the possibility of a trustworthy preoperative diagnosis of pancreatic mature cystic teratoma seems hard to be achieved. In the literature, three cases of preoperative diagnosis of dermoid cyst by FNA cytology were reported. In one case a CT guided FNA was performed and the cytological preparation of the cyst fluid revealed nucleated and nonnucleated squamous cells, keratin debris and inflammatory cells. The reported surgical therapy for pancreatic mature cystic teratomas has included external drainage of the cyst in four cases with necessity of reintervention for persistent tumor fistula in half of the cases. One patient underwent cystogastrostomy (with unknown long term results), while all the other patients (28 of 33) received excision/resection of the lesion. After surgical resection, the reported postoperative course was uneventful in almost all the cases; only 2 patients had a course complicated by pancreatic fistula and no cases of recurrent disease in the follow-up were reported. Over the years the external drainage procedures have been abandoned because a complete healing (due to retained elements of secretory epithelium) is unlikely and the possibility of recurrence or fistula formation is increased. Conservative treatment has not been described in the literature. Until a reliable method to ensure a definitive preoperative histological diagnosis of benign nature became determined, limited surgery such as lesion's excision should be avoided. Therefore, from an oncological standpoint of view, the recommended surgical therapy for pancreatic mature cystic teratomas is radical pancreatic resection. It was presented the case of a 61-year-old man with a mature cystic teratoma of the pancreas' uncinate process, incidentally discovered at diagnostic imaging. This case highlights the difficulty to obtain a preoperative diagnosis of this pathological entity and the need of increased awareness about mature cystic teratoma when examining a pancreatic cystic lesion [592].

Cystic

Benign cystic teratoma of the pancreas often appears to be potentially malignant in preoperative staging. The final diagnosis is generally obtained after surgical removal. Reliable prediction is mandatory for differential treatment. A Medline query was performed for the terms cystic teratoma, dermoid cyst and pancreas. Data were analyzed for patient characteristics, clinical appearance, diagnostic findings, therapy and follow-up. Including a new case, 26 cases of pancreatic cystic teratoma were identified. The majority of patients were symptomatic by unspecific gastrointestinal complaints. Up to date, imaging techniques fail at a distinct preoperative diagnosis. Surgical treatment evolved from various drainage and excision procedures into radical resection. Despite the strictly benign nature of cystic teratoma, oncologic resection is mostly inevitable due to difficult preoperative diagnosis. No reliable predictive marker was found to allow for organ- or parenchyma-preserving procedures. Therefore, surgery remains the treatment of choice to exclude malignancy [593].

GIST

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the gastrointestinal tract and occur rarely in the duodenum. Splenic angiosarcoma is an aggressive neoplasm with an extremely poor prognosis. It was reported a case of a 70-yearold man hospitalized for abdominal pain in the upper quadrants, dyspepsia and nausea, previously treated for Hodgkin lymphoma 30 years ago. Abdominal CT showed a solid nodular lesion in the third portion of the duodenum, the presence of retropancreatic, aortic and caval lymph nodes, and four nodular splenic masses. ¹¹¹In-octreotide scintigraphy revealed pathological tissue accumulation in the duodenal region, and in the retropancreatic, retroduodenal, aortic and caval lymph nodes, suggesting a nonfunctioning neuroendocrine peripancreatic tumor. At exploratory laparotomy, an exophytic soft tumor was found originating from the third portion of the duodenum. Pancreas-preserving duodenectomy with duodenojejunostomy, splenectomy and lymphnodectomy of retropancreatic aortic and caval lymph nodes were performed. Pathological evaluation and immunohistochemical studies showed the presence of a duodenal gastrointestinal stromal tumor with low mitotic activity and a well-differentiated angiosarcoma localized to the spleen and invading lymph nodes. It was speculated that the angiosarcoma and duodenal gastrointestinal stromal tumors of this patient were due to the treatment of Hodgkin lymphoma with radiotherapy 30 years ago. Pancreas-preserving segmental duodenectomy can be used to treat non-malignant neoplasms of the duodenum and avoid extensive surgery. Splenectomy is the treatment of choice for localized angiosarcomas but a strict follow-up is mandatory because of the possibility of recurrence [594].

Primary extragastrointestinal stromal tumors (EGISTs) arising in the pancreas are extremely rare, with only ten cases documented to our knowledge. It was ed a further case of EGIST of the pancreas. The patient was a 55-year-old man who presented with postprandial abdominal discomfort. Abdominal computed tomography and magnetic resonance imaging showed a lobulated heterogenous enhancing mass, 11 cm in diameter, in the abdominal cavity. No regional lymphadenopathy, ascites, or metastasis was seen radiologically. There was no obvious lesion in the stomach or small intestine. The initial diagnosis was a solid pseudopapillary tumor or serous cystic neoplasm. The patient underwent distal pancreatectomy with splenectomy. Microscopically, the tumor consisted of spindle cells arranged in short fascicles. Mitotic figures were seen in 7/50 high-power fields. Immunohistochemical examination revealed strongly positive staining for CD117. Based on these findings, the final pathologic diagnosis was a primary EGIST of the pancreas. This case consolidates the possibility that this rare tumor can involve the pancreas as a primary site and should be included in the differential diagnosis of cystic lesions in this site [595].

Schwannoma

Pancreatic schwannomas are rare neoplasms that originate from Schwann cells. In 1910, Verocay reported a schwannoma as a true neoplasm which originated from Schwann cells. and which did not contain neuroganglion cells. Since then, schwannomas have become well known as benign spindle cell tumors derived from Schwann cells that line the nerve sheaths. Pancreatic schwannomas arise from either autonomic sympathetic or parasympathetic fibers, both of which course through the pancreas as branches of the vagus nerve. The Schwann cells line the nerve sheath and can generate either schwannoma or neurofibroma. Schwannoma usually occur in the extremities, but can also be found in the trunk, head and neck, retroperitoneum, mediastinum, pelvis and rectum. Pancreatic schwannomas are even more unusual neoplasms that affect adults with an equal gender distribution. These tumors vary considerably in size and approximately two-thirds are reported to undergo degenerative changes including cyst formation, calcification, hemorrhage, hyalinization and xanthomatous infiltration. As a result, they may radiographically mimic cystic pancreatic lesions (e.g. mucinous cystic neoplasms, solid and pseudopapillary neoplasms, serous cystic neoplasms, and pseudocysts). Microscopically, a typical schwannoma is composed of 2 areas, namely Antoni A and Antoni B areas. The Antoni A area is hypercellular and characterized by closely packed spindle cells with occasional nuclear palisading and Verocay bodies, whereas the Antoni B area is hypocellular and is occupied by loosely arranged tumor cells. Most of the pancreatic schwannomas reported had both Antoni A and Antoni B areas in various proportions. Degenerative or cystic changes such as calcification or hemorrhage are often recognized in the Antoni B area. These changes result from vascular thrombosis and subsequent necrosis. Cystic pancreatic schwannomas can mimic the whole spectrum of cystic pancreatic lesions including: intraductal mucinous-papillary neoplasms, mucinous cystic neoplasms, serous cystic neoplasms, solid and pseudo-papillary neoplasms, lymphangiomas, and pancreatic pseudocysts. Immunohistochemically, schwannomas stain strongly positive for S-100 protein, vimentin and CD 56, while negative for other tumor markers including cytokeratin AE1/AE3, desmin, smooth muscle myosin, CD 34 and CD 117. Authors briefly describe a 64-year-old female patient with cystic pancreatic schwannoma mimicking other cystic tumors and review the literature. Databases for PubMed were searched for English-language articles from 1980 to 2010 using a list of keywords, as well as references from review articles. Only 41 articles, including 47 cases, have been reported in the English literature. The mean age was 56 years (range 20-87 years), with 45 percent of patients being male. Thirty percent of patients were asymptomatic and 70 percent of patients were symptomatic. Symptoms included abdominal pain (57 %), weight loss (13 %), back pain (6%), nausea/vomiting (4%), abdominal mass (4%), melena (4%), and jaundice (4%). The symptoms did not correlate with tumor size and tumor location. Mean tumor size was 6 cm (range 1-20 cm). Tumor location was the head (40 %), head and body (6 %), body (21 %), body and tail (15 %), tail (4 %), and uncinate process (13 %). Thirty-four percent of patients exhibited solid tumors and 60 percent of patients exhibited cystic tumors. Since malignant transformation of pancreatic schwannomas is uncommon, simple enucleation is usually sufficient. Treatment included pancreaticoduodenectomy (32 %), distal pancreatectomy (21 %), enucleation (15 %), unresectable (4 %), refused operation (2 %) and the detail of resection was not specified in 26 percent of patients. No patients died of disease with a mean follow-up of 16 months (range 3-65 months), although 5 (11 %) patients had a malignancy. No patient died of disease with a follow-up of 16 months (range 3-65 months), although 4 (9 %) patients had a malignancy. The tumor size was significantly related to malignant tumor (14 \pm 6 cm for malignancy vs 6 \pm 4 cm for benign) and cystic formation (8 \pm 6 cm for cystic tumor vs 4 ± 2 cm for solid tumor). The preoperative diagnosis of pancreatic schwannoma remains difficult. An intraoperative frozen section should be performed, as it helps to establish the diagnosis of a benign schwannoma and avoid more radical resection. Large tumors, tumors involving portal vein, ampulla, or splenic hilum, may require a more radical resection than simple enucleation. Cystic pancreatic schwannomas should be considered in the differential diagnosis of cystic neoplasms and pseudocysts. In the

forwarded case, intraoperative frozen section confirmed the diagnosis of a schwannoma. In conclusion, pancreatic schwannomas deserve attention with regard to the differential diagnosis of pancreatic lesions. Preoperative diagnosis is very difficult. Simple enucleation is adequate if this is possible to achieve. Intraoperative frozen section is useful to diagnose schwannoma [596].

Schwannomas are benign tumors that arise from neural sheath Schwann cells. Solitary benign schwannoma is generally located in the head and neck and is a rare neoplasm among the tumors of the retroperitoneal space. Reports of laparoscopic excision of retroperitoneal schwannomas have recently been on the increase. However, few cases of single-port laparoscopic excision of these tumors have been reported. Moreover, there are no reports of single-port excision of schwannomas attached to the body of pancreas and around the splenic vessels. This was the first report of a schwannoma lying adjacent to the body of the pancreas between the splenic artery and vein that was excised by single-port laparoscopic surgery. The most notable aspect of the procedure is the use of bipolar forceps. Single-port laparoscopic excision using bipolar forceps is a feasible and safe procedure for retroperitoneal solitary tumors, even when they are close to the splenic artery and vein [597].

It was reported on a Schwannoma of the third portion of the duodenum that was operated with an en bloc resection with inclusion of the uncinate process of the pancreas [598].

Neurofibroma

Neurofibromas arise from peripheral nerve cells. They are rarely found within the pancreas, especially not associated with type I neurofibromatosis. It was reported a case of a neurofibroma in a 44-year-old woman who initially presented with epigastralgia. Imaging revealed one large cystic mass of $5.7 \times 8 \times 5.8$ cm in the pancreatic body, which was resected with distal pancreatectomy. The postoperative course of treatment was without complication, and no signs of recurrence were observed after 1 year and 6 months' follow-up [599].

Inflammatory pseudotumor

Inflammatory pseudotumor of the spleen is an uncommon benign mass-like lesion. It can occur in an accessory spleen, which may be found rarely in the pancreas tail. It was reported a case of a 51-year-old woman with an inflammatory pseudotumor of the intrapancreatic accessory spleen mimicking a fibrous pancreatic mass with hemosiderin deposition. This is the first case report including radiological and histopathological findings of this extremely rare condition. In conclusion, inflammatory pseudotumor of an intrapancreatic accessory spleen should be regarded as a differential diagnosis in the case of a fibrotic mass with hemosiderin deposition deposition located in the pancreas tail [600].

Lymphoepithelial cysts

It was reported an association of lymphoepithelial cysts (LEC) of the pancreas with Human Immunodeficiency Virus (HIV) infection. An association between LEC and HIV infection is already established in the parotid gland (PG). The report of the first two cases of LEC of the pancreas associated with HIV infection and comparison of the clinical and histopathological aspects of LECs of the pancreas and of the PG described that LECs of the pancreas were discovered by CT imaging in 2 patients with a history of HIV infection. Notably, LEC completely resolved in one patient after initiation of antiretroviral therapy. This is the first

report of an association of LEC of the pancreas and HIV infection. In the presence of LEC of the pancreas, it was proposed a systematic screening for HIV infection and associated lesions in the PG. Antiretroviral therapy should be initiated in untreated patients. Surgery should be reserved for symptomatic patients in whom medical therapy has failed [601].

Pancreatic amyloidosis

Amyloidosis is a systemic disease that is characterized by the deposition of fibrillary proteins in different organs. Primary, secondary, and familial forms of amyloidosis are defined in the literature. The primary form is a plasma cell dyscrasia in which a light chain of an immunoglobulin is deposited. Secondary amyloidosis is due to chronic disease such as diabetes mellitus (DM), rheumatoid arthritis, and sarcoidosis. Amyloid is produced from serum amyloid A (SAA), which is a acute-phase protein. The familial form is a group of autosomal-dominant disease in which a mutant protein is produced. Although amyloidosis frequently affects multiple organs, localized forms were also reported. The histopathological features of pancreatic amyloidosis have been well defined in the literature: however, radiologic findings were rarely reported. In one report it was presented imaging findings of a patient with primary amyloidosis of pancreatic islet cells. Imaging findings of amyloidosis in several organs represent a wide spectrum since they can vary due to the type of amyloidosis (primary or secondary) and the degree of involvement. Primary amyloidosis may affect visceral organs in the abdomen including the liver, spleen, pancreas, and kidneys. Also, mesentery and retroperitoneal space may be affected in amyloidosis. Pancreatic involvement of amyloidosis was described in the literature mainly with histopathological findings. Due to these reports, pancreatic amyloidosis can be seen as diffuse infiltration of exocrine and endocrine pancreas. The endocrine part of pancreas is a frequent site of involvement in secondary amyloidosis and this is mainly due to the presence of type 2 DM. In a newly presented case, US findings were compatible with previous reports. Diffuse hypoechogenicity of the pancreas might be due to diffuse involvement of the pancreas. However, CT findings were interesting; it was not seen any disease in the records, which may enlarge the pancreas as seen in this patient. Diffuse infiltration of the pancreatic parenchyma may be seen in lymphoma, but the presence of multiple calcification and lack of accompanying lymphadenopathies excluded this entity in the differential diagnosis. Autoimmune pancreatitis is another entity that must be included in the differential diagnosis of diffuse pancreatic enlargement and infiltration. However auto-immune pancreatitis characteristically causes a hypodense rim around the pancreas. Also, increased amounts of IgG4 is a strong indicator of autoimmune pancreatitis with appropriate imaging findings. CT findings of our patient did not show either hypodense rim around the pancreas nor other inflammatory changes. Also, calcification is rarely seen in auto-immune pancreatitis. Acute inflammatory pancreatitis also may be investigated on patients with diffuse enlargement of the pancreas. However, the absence of pancreatic duct dilatation and lack of peripancreatic fat obliteration excluded the diagnosis of acute pancreatitis, with normal amylase levels in our case. Another feature of this case was the point that amyloidosis may mimic the ampulla Vater tumor on endoscopy by disseminating from pancreas to the papilla. Cross sectional imaging is important in these situations in order to prevent misdiagnosis. Loss of hyperintense signal of pancreas parenchyma with primary amyloidosis on T1-weighted image was reported previously. Decreased signal intensity on T1-weighted images may be seen in diffuse pancreatitis, diffuse involvement of pancreas in tuberculosis, as well as lymphoma and autoimmune pancreatitis. Inflammatory pancreatitis, pancreatic lymphoma, and autoimmune pancreatitis may be excluded in differential diagnosis according to other imaging findings mentioned above. Increased signal intensity in pancreas and narrowing of pancreatic duct are seen in diffuse involvement of the pancreas in tuberculosis, which was absent in our case. Though imaging methods and laboratory findings may suggest a diagnosis or exclude some diseases affecting pancreas histopathological confirmation of amyloidosis is necessary. In our case, only Langerhans island cells were affected from

amyloidosis and exocrine pancreas did not show any amyloid infiltration. To the best of knowledge, this is the first report that specifically describes imaging findings of islet cell amyloidosis. Previous reports described the pancreatic amyloidosis without discrimination of endocrine and exocrine pancreas amyloidosis. It was shown that islet cell amyloidosis may be a cause of type 2 DM. Islet amyloid is present in > 90 percent of patients with type 2 DM. Recent data, particularly from transgenic mouse studies, indicate that islet amyloidosis is a diabetogenic factor, which is both a consequence (of insulin resistance) and cause (of betacell failure) of type 2 DM. Amyloid deposition, commonly seen in the pancreas of patients with type 2 DM, is generally classified as local amyloidosis may be included in the differential diagnosis of diffuse pancreatic enlargement mimicking pancreatitis. Absence of laboratory findings indicating acute pancreatitis, and abnormally enlarged pancreas may be seen in pancreatic amyloidosis. Imaging features of pancreatic amyloidosis on US, CT and MRI may alert radiologists and clinicians for the probability of DM development before prominent laboratory findings and clinical features [602].

Metastases to pancreas

Metastases to the pancreas are rare; nevertheless, early detection allows for appropriate treatment and improved outcomes for metastatic disease. Computed tomography plays a pivotal role in characterizing these tumors, as demonstrated in this pictorial review. Given significant differences in prognosis and treatment, it is crucial to differentiate primary and secondary pancreatic lesions; however, this may not be possible based on imaging features alone [603].

Metastasis to the pancreas is uncommon. Several types of cancers were reported to metastasize to the pancreas. Surgery is advocated in selected patients when technically feasible and if the patient can be rendered disease free. A retrospective review of metastasis to the pancreas patients was performed over a 7-year time period. Twenty patients with a median age of 63 years were identified. Fifteen patients (75 %) were males and (50 %) presented with abdominal pain. Nine patients (45 %) were offered surgical resection, distal pancreatectomy was the most common procedure (n=4). The commonest pathology was RCC (60 %), followed by lung (20 %), colon (15 %), and breast (5 %). Median disease free interval (DFI) was 96 months for RCC, 7 months for other pathologies. Median survival was 19 months for RCC, 8.5 months for other pathologies. Based on DFI, short DFI patients (\leq 12) months) had worse prognosis (2-year survival of 40 %), as opposed to (2-year survival of 80 %) in longer DFI patients. RCC patients with a DFI longer than 94 months had a better survival. Survival of resected PM tended to be longer than non-resected metastases. Pancreatic metastases from RCC carries a consistently favorable prognosis compared to other pathologies. Surgical resection of pancreatic metastases is a safe and viable option, and, in selected patients, may improve survival. However, a period of expectant management in patients with short DFI may be considered [604].

Metastatic carcinoma of the pancreas from another primary site is uncommon and it accounts for 2-5 percent of all pancreatic cancer cases. It was reported the case of one patient with pancreatic metastasis from colon carcinoma in the past and would like to add another six cases of pancreatic metastases from different types of cancer. The diagnosis of cancer metastatic to the pancreas should be suspected when patients have a history of malignancy, especially of kidney, skin, lung, colon and breast cancer. Besides imaging studies, such as computed tomography (CT) scan, bone scan and positron emission tomography (PET)/CT scan, endoscopic ultrasound (EUS)-guided biopsy has most value in ruling out second primary pancreatic cancer. The prognosis of pancreatic metastases is

essentially determined by the underlying primary cancer and the potential treatment options [605].

Fine needle biopsy

The study was performed to determine the frequency and origin for metastatic disease to the pancreas as found in an endoscopic ultrasound directed fine-needle aspiration series. The records were electronically searched for all fine-needle aspirates obtained from pancreatic masses between 2002 and 2010. All cases with a diagnosis of metastatic disease were reviewed and whenever possible correlated with subsequent resection specimens. A total of 17 metastatic malignancies to the pancreas were detected in pancreatic FNAs representing 0.7 percent of all cases. Primaries included eight renal cell carcinomas, one medullary carcinoma of the thyroid, four lymphomas, one alveolar rhabdomyosarcoma, one squamous cell carcinoma derived from the esophagus, and a second squamous cell carcinoma originating from a lung primary and a small cell carcinoma of the lung. Metastatic renal cell carcinoma was the most frequent metastasis to the pancreas representing 47 percent of metastatic lesions detected by FNA. The metastatic deposits could be detected in the pancreas as many as 10 years following the original diagnosis and resection of the renal cell carcinoma [606].

Surgery

One study tried to clarify the role of pancreatic resection in the treatment of secondary malignancy with metastasis or local invasion to the pancreas in terms of surgical risk and survival benefit. Data of secondary malignancy of the pancreas from 19 patients and cases reported in the English literature were pooled together for analysis. There were 329 cases of resected secondary malignancy of the pancreas, including 241 cases of metastasis and 88 cases of local invasion. The most common primary tumor metastatic to the pancreas and amenable to resection was renal cell carcinoma (RCC) (74 %). More than half (52 %) of the primary cancers with local invasion to the pancreas were colon cancer, and nearly half (41 %) were stomach cancer. The median metastatic interval was 84 months (7 years) for overall primary tumors and 108 months (9 years) for RCC. The 5-year survival for secondary malignancy of the pancreas after resection was 61 percent for metastasis and 59 percent for local invasion, with 73 percent for RCC metastasis, 69 percent for colon cancer, and 4 for stomach cancer with local invasion to the pancreas. Pancreatic resection should not be precluded for secondary malignancy of the pancreas because long-term survival could be achieved with acceptable surgical risk in selected patients [607].

From kidney

Natural history of renal cell carcinoma includes metastases to the pancreas. The literature reports that selected patients may have benefits by pancreatic resection in terms of long term survival. It was reported patient outcome and considerations on immunotherapy approach. From 2001 to 2010 eight patients underwent pancreatic resection for metastases from renal cancer. We reviewed surgical outcome and following treatment (conventional chemotherapy: 5FU-Vindesine; Immunotherapy: Interleukin 2 – interferon – dendritic cells) of these patients. All patients underwent radical pancreatic resection (7 spleno-pancreatectomies; 1 segmental pancreatic resection) and were R0 after surgery. No postoperative mortality was reported. Morbidity was 37% (2 distal leakage; 1 pneumonitis). Two patients did not receive any further treatment; 2 patients received conventional chemotherapy; 2 patients received immunotherapy (interleukin2 + interferon); 2 patients received dendritic cells (DC) interleukin-2 infusion. Three years overall survival rate was 55 percent. Disease free survival after 3 years was 30 percent. The data confirm that pancreatic resection should be offered to selected patients with no mortality and low morbidity. Long-term survival is achievable, but

recurrence rate after surgery is high. Immunotherapy could be effective to control tumour progression especially in selected cases where DC may be used [608].

An 81-year-old man presented with jaundice and a pancreatic tumor. 6 years ago transperitoneal nephrectomy had been performed because of a clear cell renal cancer (pT3b pN0 pM0). Laboratory tests showed normocytic anemia and signs of cholestasis. Abdominal ultrasonography revealed a well-defined mass of the head of the pancreas with a diameter of about 4 cm, and a previously diagnosed adrenal mass which had slightly increased in size. Contrast-enhanced ultrasound demonstrated a hyperenhancing of the pancreatic mass, untypical for primary adenocarcinoma of the pancreas. Endoscopic ultrasound-guided fine-needle aspiration disclosed a metastasis of the previously resected renal cancer. Bilary spincterotomy and stent insertion were performed. Because of proven pancreatic metastasis and suspected adrenal metastasis of renal cancer palliative treatment with multi-targeted receptor tyrosine kinase inhibitor sunitinib was initiated. It was concluded that renal cell carcinomas are the most common primary tumors leading to pancreatic metastasis. In contrast to ductal adenocarcinoma pancreatic metastasis shows hyperenhancement when examined by using contrast-enhanced ultrasonography. Endoscopic ultrasound-guided fine-needle aspiration helps to confirm the suspected diagnosis [609].

From urinary bladder

Micropapillary carcinoma of the bladder is an extremely aggressive variant of urothelial carcinoma. Radical cystectomy is the standard treatment for all patients, including those with nonmuscle-invasive disease. It was presented a patient diagnosed with clinical Stage T1 micropapillary carcinoma of the bladder who was found to have a 2-cm metastasis to the head of the pancreas. This case represents the first report of a solitary metastatic urothelial carcinoma to the pancreas [610].

From thyroid

Lungs and bones are the most common sites for distant metastases from papillary thyroid cancer (PTC). Metastases to the pancreas are extremely rare. It was presented a man with pancreatic metastases from PTC. A 56-year-old man underwent total thyroidectomy, rightmodified neck dissection, and radioactive iodine (RAI) remnant ablation for PTC at age 47 years (in 2002). Between 2002 and 2007, he had three more neck surgeries, two RAI therapies, and external beam radiotherapy for persistent and subsequently metastatic PTC. In 2008, a computed tomography/positron emission tomography (CT/PET) scan showed an 18F-fluorodeoxyglucose (FDG)-avid pancreatic focus. Magnetic resonance imaging (MRI) revealed a pancreatic nodule at the same location. An EUS-guided biopsy confirmed the diagnosis of pancreatic metastasis from PTC, and molecular studies showed positive BRAF(V600E) mutation. He was treated with sorafenib for 6 months. Although a lung CT scan done 2 months after initiation of sorafenib suggested stability of the disease, MRI studies done at 3 and 6 months showed clear progression with an increase in the size of the lung and pancreatic metastases. Subsequently, he developed liver, bone, and omental metastases. He died in 2011, 9 years and 8 months after the initial diagnosis of PTC and 20 months after discovery of the pancreatic metastasis [611].

Lungs and bones are the most common sites for distant metastases from papillary thyroid cancer (PTC). Metastases to the pancreas are extremely rare. It was presented a man with pancreatic metastases from PTC, report our experience with sorafenib therapy, and discuss the role of endoscopic ultrasound (EUS)-guided biopsy in its diagnosis. In summary a middle-aged man with PTC developed lung metastases despite multiple surgeries and radioactive iodine (RAI) therapies. Seven years after the initial diagnosis, a pancreatic metastasis was accidentally discovered. Both the metastasis and the primary thyroid tumor

are positive for BRAF(V600E) mutation. The lung and pancreatic metastases progressed while the patient was receiving sorafenib for 6 months, and the patient died 20 months after diagnosis of pancreatic metastasis. It was concluded that PTC rarely metastasizes to the pancreas. In this patient, an FDG PET scan and EUS-guided biopsy played important roles in the diagnosis. PTC metastases to the pancreas usually occur in otherwise advanced disease. In the patient presented here, sorafenib may have slowed disease progression but the overall utility of tyrosine kinase inhibitors in pancreatic metastases from PTC is not clear [612].

From uterus

Uterine leiomyosarcoma is an aggressive malignant tumor that often leads to metastatic dissemination, generally in the lungs, liver, brain, and bones. Despite the fact that pancreatic neoplasms spread easily, the pancreas is not a usual target organ from other neoplasms. It was presented a rare case of metastasis to the pancreas from uterine leiomyosarcoma treated with segmental resection with no recurrence at this stage. A review of the literature is later presented showing no similar case to what has been reported. Surgical resection of unique pancreatic metastases is a safe practice. An increase in the survival rate has been demonstrated after resection of metastases from renal cell carcinoma, although it has not been proved with metastases from other locations [613].

From leiomyosarcoma

Metastases to the pancreas gland are uncommon, especially from leiomyosarcoma. It was reported a case of asymptomatic pancreatic metastasis resection of leiomyosarcoma. A 59-year-old patient was treated for thighbone leiomyosarcoma, with surgical resection and adjuvant radiotherapy. After 4 years of follow-up, although that patient was asymptomatic, a pancreatic metastasis was identified by CT and fine needle aspiration. Open left pancreatectomy was performed [614].

Metastase from pancreatic cancer

To inner genitalia

A case is presented of pancreatic tail carcinoma metastasizing to the uterus, right ovary and right sacrouterine ligament 2.5 years after the primary tumor had been detected and treated. During explorative laparotomy, performed after 3D color Doppler ultrasonographic visualization of a suspected finding in the right adnexal region, metastatic deposits in the uterus, right ovary, right sacrouterine ligament and right ureter originating from the primary adenocarcinoma of the tail of the pancreas were detected and surgically removed [615].

PANCREATIC ENDOCRINOLOGY AND ENDOCRINE TUMORS

Guidelines

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NET)s update previous guidance published in 2005. They have been revised by a group who are members of the UK and Ireland Neuroendocrine Tumour Society with endorsement from the clinical committees of the British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland (and its Surgical Specialty Associations), the British Society of Gastrointestinal and Abdominal Radiology and others. The authorship represents leaders of the various groups in the UK and Ireland Neuroendocrine Tumour Society, but a large amount of work has been carried out by other specialists, many of whom attended a guidelines conference in 2009. It was attempted to represent this work in the acknowledgements section. Over the past few years, there have been advances in the management of neuroendocrine tumours, which have included clearer characterisation, more specific and therapeutically relevant diagnosis, and improved treatments. However, there remain few randomised trials in the field and the disease is uncommon, hence all evidence must be considered weak in comparison with other more common cancers [616].

Genomics

Functional genomics, the analysis of the wealth of data produced by genome-wide analyses of gene expression, protein-protein, and protein-DNA interactions, has revolutionized biomedical research. The ability to determine global gene expression profiles, transcription factor-binding sites, and histone modification maps using microarray-based technologies and next-generation sequencing applications has greatly enhanced our understanding of gene regulatory networks and the molecular wiring diagrams of cells and tissues. The organogenesis of the endocrine pancreas involves numerous signaling events within the endoderm-derived pancreatic epithelium and the surrounding mesenchyme, as well as complex transcription factor networks. Detailed understanding of the differentiation process from foregut endoderm to mature endocrine cells has enabled the rational design of in vitro differentiation protocols that coax embryonic stem cells into beta-like cells that might enable cell replacement therapy for diabetes in the future. In one review, it was summarized the research studies that have utilized genomic tools to elucidate endocrine pancreatic organogenesis [617].

Staging systems

Both the European Neuroendocrine Tumor Society (ENETS) and the International Union for Control/American Joint Cancer Committee/World Health Cancer Organization (UICC/AJCC/WHO) have proposed TNM staging systems for pancreatic neuroendocrine neoplasms. One study aimed to identify the most accurate and useful TNM system for pancreatic neuroendocrine neoplasms. The study included 1072 patients who had undergone previous surgery for their cancer and for which at least 2 years of follow-up from 1990 to 2007 was available. Data on 28 variables were collected, and the performance of the two TNM staging systems was compared by Cox regression analysis and multivariable analyses. All statistical tests were two-sided. Differences in distribution of sex and age were observed for the ENETS TNM staging system. At Cox regression analysis, only the ENETS TNM staging system perfectly allocated patients into four statistically significantly different and equally populated risk groups (with stage I as the reference; stage II hazard ratio [HR] of

death 16; stage III HR of death 52; and stage IV HR of death 160). However, the UICC/AJCC/WHO 2010 TNM staging system compressed the disease into three differently populated classes, with most patients in stage I, and with the patients being equally distributed into stages II-III (statistically similar) and IV (with stage I as the reference; stage II HR of death 10; stage III HR of death 9; and stage IV HR of death 31). Multivariable modeling indicated curative surgery, TNM staging, and grading were effective predictors of death, and grading was the second most effective independent predictor of survival in the absence of staging information. Though both TNM staging systems were independent predictors of survival, the UICC/AJCC/WHO 2010 TNM stages showed very large 95 percent confidence intervals for each stage, indicating an inaccurate predictive ability. The data suggest the ENETS TNM staging system is superior to the UICC/AJCC/WHO 2010 TNM staging system and supports its use in clinical practice [618].

Diagnostics

MRI

To investigate the added value of fusion of high b-value diffusion-weighted images (DWI) and T2-weighted (T2) MR images for the detection of pancreatic neuroendocrine tumors (PNT) 18 patients with 18 histologically proven PNT were studied. Two radiologists independently and retrospectively reviewed four randomized images sets (T2+T1, DWI, T2+DWI, and DWI+T2 fusion). Lesion detection confidence level was assessed using a three grade score (no lesion; uncertain lesion and certain lesion); lesion size and signal intensity were recorded. Apparent diffusion coefficients (ADC) of tumor and adjacent pancreas were measured. Readers 1 and 2 respectively detected 14/18 and 16/18 lesions on T2+T1, 13/18 and 12/18 on DWI, 16/18 and 15/18 on T2+DWI and 17/18 and 16/18 on DWI+T2 fusion. Lesion median size was 16 mm (range: 7 mm-40 mm), 22 percent were hyperfunctioning (all insulinomas) and 72 percent were low-grade (Rindi 1). All tumors except one (with cystic component) showed lower ADC than adjacent pancreatic parenchyma. Fusion imaging had significantly better detection score by both authors and provided the higher inter-reader agreement (kappa 0.7). DWI alone had the worst score for both readers. Fusion images improve the detection of PNT, especially in patients with small isointense lesions on conventional MR sequences [619].

Chromogranin A

Chromogranin A is a very sensitive but relatively nonspecific serum marker of GEP-NENs. False high values are found, for instance, in patients with renal insufficiency or severe malabsorption syndrome. Chromogranin A determination is useful for staging and prognosis, since the serum concentration correlates to the tumor mass. Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are a heterogeneous group of neoplasms that arise from neuroendocrine cells of the GI tract and pancreas. Due to the lack of symptoms in the early stage of the disease and the frequency of nonspecific gastrointestinal symptoms, GEP-NETs are difficult to diagnose. This delay in diagnosis often results in patients presenting with advanced disease and thus a poor prognosis. There is an unmet medical need for earlier, more definitive GEP-NET diagnosis. Identification of effective biomarkers to improve GEP-NET diagnosis, as well as to assess treatment efficacy, relapse and prognosis, is important for improving outcomes in GEP-NET. Chromogranin A is currently the most useful general biomarker for the assessment of GEP-NET. One review summarized the biochemical characteristics of chromogranin A, its specificity and sensitivity for GEP-NET diagnosis, and its use in monitoring treatment effectiveness, disease progression and prognosis [620].

⁶⁸Ga-DOTA-TOC

To characterize a commonly occurring increased uptake by the uncinate process of the pancreas at PET/CT using 68Ga-DOTA-d-Phe1-Tyr3-octreotide (68Ga-DOTA-TOC). This tracer has replaced In pentetreotide (OctreoScan®) for somatostatin receptor scintigraphy at one laboratory. Fifty of the first 74 PET/CT examinations with 68Ga-DOTA-TOC could be evaluated in retrospect. None of these patients had surgery or showed any pathology in the pancreas head at the concomitant CT. Thirty-five of the 50 examinations (70 %) showed an uptake by the uncinate process sufficiently intense to be interpreted as pathologic and simulating a tumor. Mean SUVmax was 9.2. Mean SUVmean using an isoactivity cut-off of >75 percent and >50 percent was 7.8 and 6.0, respectively. Volume calculations of the uncinate process activity using these definitions gave 0.9 mL and 4.2 mL, respectively. There is a frequent physiological uptake of 68Ga-DOTA-TOC by the pancreas uncinate process. This may be caused by an accumulation of pancreatic polypeptide-containing cells expressing somatostatin receptors. If there is a normal finding at concomitant diagnostic CT, this uptake should be regarded as physiological [621].

Gallium-68 (Ga-68) DOTA-1-Nal3-octreotide (DOTA-NOC) positron emission tomography (PET)/computed tomography (CT) is increasingly used for neuroendocrine tumors (NETs), often found primarily in the pancreas. However, physiologic uptake of DOTA-NOC has been described in the uncinate process of the pancreas. It was studied DOTA-NOC uptake in this organ. Ninety-six patients underwent 103 DOTA-NOC scans, with pathology-proven pancreatic NET (n=40) and nonpancreatic NET or biochemical suspicion of NET (n=63). DOTA-NOC uptake was detected in 35 documented pancreatic tumor sites (SUV: 5.5-165; mean: 25.7 \pm 28.8; median: 17.8). Among 63 cases without previous known pathology, uptake was suspicious for tumor in 24 sites (SUV: 4.7-35; mean 16.3 \pm 8.0; median: 14.1), and in 38 sites, it was judged as physiological, generally lower relative to adjacent structures (SUV: 2.2-12.6; mean: 6.6 \pm 2.2; median: 6.2). In 24 scans with suspected tumor and in 37 of 38 scans with physiological uptake, diagnostic computed tomography or magnetic resonance imaging or endoscopic ultrasonography failed to detect tumor. It was concluded that pancreatic DOTA-NOC uptake must be interpreted with caution, and further studies are required [622].

Insulinoma

Endogenic hyperinsulinism is mainly caused by neuroendocrine tumors (insulinomas) which autonomously secrete insulin. Because the symptoms are often aspecific, a considerably delay in diagnosis occurs. The treatment consists of operative removal of the tumor from the pancreas, preceded by pre-operative localization. In this article we describe our experience with surgical removal of insulinomas. It was retrospectively analyzed all patients with insulinoma which were treated in one center. Definitive diagnosis was made using a 72hours glucoses fasting test. Between 2002 and 2011, 45 patients (36 % men and 64 % female) were treated. The most prevalent symptoms were altered consciousness and general malaise. The combination of CT-scan and endoscopic ultrasound had the highest (90%) sensitivity to localize tumors pre-operatively. During surgery, in 40 patients (89%) the tumor could be removed by enucleation. In the other five patients partial pancreas resection was required. In 22 patients (49 %) it was used intra-operative insulin level measurements to confirm complete tumor resection. Within the first month after surgery, two patients (4 %) developed acute pancreatitis, and four patients (9 %) developed a pancreatic fistula. One patient died of multi-organ-failure. All patients were free from symptoms of hyperinsulinism after the surgery and after a median follow-up of 5 years. It was concluded that based on the experience with 45 patients, surgical removal, aided by pre-operative localization with CT and endoscopic ultrasonography, is an effective and safe treatment for insulinomas [623].

VIP and calcitonin-producing pancreatic tumor

Pancreatic neuroendocrine tumor (pNET) secretes various peptide hormones; however, calcitonin hypersecretion is rare. Its clinicopathological significance and treatment is still controversial. A 43 year-old Japanese man presented severe watery diarrhea and a large mass in the pancreatic tail. Blood concentration of VIP was elevated to 649 pg/mL (reference range: 0-100 pg/mL), and calcitonin to 66,700 pg/mL (reference range: 15-86 pg/mL). There was no tumor in other endocrine organs. The resected tumor was composed of 80 percent calcitonin-positive cells and 10 percent VIP-positive cells. After the operation, the levels of VIP and calcitonin were decreased to 44 and 553 pg/mL, respectively, and diarrhea was improved. The mRNA of somatostatin receptor (SSTR) subtypes 2, 3 and 5 in the tumor tissue were increased 22.8, 25.1, and 37.0-fold of those of normal pancreas, respectively. At 19 months after the operation, blood calcitonin was again raised to 3,980 pg/mL, and metastatic tumors were found in the liver. With the treatment of long-acting somatostatin analogue, calcitonin was reduced to 803 pg/mL. The patient does not present endocrine symptom, and the size of the metastatic tumors appears stable. From the world literature to date, co-secretion of VIP and calcitonin was documented in only 10 cases of pNET including the current case. Although VIP is a primary cause of diarrhea in these cases, high level of calcitonin may also influence on the clinical symptoms. Somatostatin analogue suppresses the levels of VIP and calcitonin, and the control proliferation is also expected when tumor cells express SSTRs [624].

MEN 1

Many serologic and radiographic modalities are used for monitoring multiple endocrine neoplasia type 1 (MEN 1) patients for pancreaticoduodenal neuroendocrine tumors (PNETs). It was compared serum markers and imaging studies obtained preoperatively with the gross pathology and immunohistochemical findings and correlated preoperative testing with postoperative outcome. From 2000 to 2008, 52 MEN 1 patients (62 % female; median age 43 years) underwent 56 pancreatic operations (88 % distal pancreatectomies) for suspected PNETs. Preoperative serum markers (human pancreatic polypeptide, HPP), gastrin, and glucagon] and imaging (CT, ¹¹¹In pentetreotide scintigraphy, and endoscopic ultrasound, EUS) were compared to the pathologic findings. Postoperative serum markers and survival were followed. Human pancreatic polypeptide had the highest agreement between an elevated serum level and positive tumor immunostaining (83 % vs 5% agreement for gastrin v. 67 % agreement for glucagon). Preoperative CT had 81 percent sensitivity and positive predictive value (PPV) of 97 percent for PNETs. ¹¹¹In pentetreotide scintigraphy had 84 percent sensitivity and PPV of 96 percent. Preoperative endoscopic ultrasonography (EUS) had 100 percent sensitivity and PPV, with close correlation between the largest lesion seen on EUS and pathology. Median follow-up was 4 years. Overall survival was 89 percent at 5-year follow-up. The study substantiates EUS as providing the highest preoperative sensitivity and PPV in assessing the presence of PNETs in MEN 1 patients. CT and octreotide scintigraphy can yield both false-positive and false-negative results. HPP, gastrin, and glucagon were the most commonly measured tumor markers in our series but did not always correlate with immunostaining. With an aggressive surgical approach, satisfactory rates of biochemical improvement and long-term survival were observed [625].

Cystic pancreatic endocrine neoplasms

Cystic pancreatic endocrine neoplasms (CPENs) are uncommon tumors with uncertain disease biology and ill-defined diagnostic features. A prospectively maintained pancreatic

cyst registry was gueried, and 31 cases of CPEN that were resected between 1995 and 2010 were identified. Patient and lesion characteristics were detailed and compared with resected non-PEN cystic lesions. Recurrence and survival outcome were compared with 31 noncystic PENs matched for functional status, differentiation, size, World Health Organization classification, grade, and presence of metastases. During the study period, CPENs accounted for 7 percent of resected pancreatic cysts (31/469) and 12 percent of resected PENs (31/255). CPENs were primarily sporadic (94 %), solitary (87 %), nonfunctioning (100 %), and incidentally discovered (68 %). The median diameter was 2.1 cm (range, 0.9-6.2 cm), and preoperative imaging identified septations in 29 percent, a solid component in 26 percent, and cyst wall enhancement or a characteristic hypervascular rim in 45 percent of cases. Preoperative imaging and/or cytology suggested the diagnosis of CPEN in 61 percent. Compared with resected nonendocrine cystic lesions, CPEN were less frequently symptomatic, less likely to contain septations, and smaller. Compared with matched noncystic PENs, CPENs had comparable demographic, radiologic, and pathologic features and statistically similar long-term outcome (5-year disease-free survival: CPEN: 100 % vs PEN: 86 %). It was concluded that in this study, CPENs were primarily asymptomatic small lesions that could be characterized in the majority of cases by cyst wall enhancement on preoperative imaging and/or cytologic assessment. No significant difference in recurrence or survival outcome was identified between cystic and noncystic PENs [626].

Extended surgery

Pancreatic endocrine tumours are often diagnosed at an advanced stage with hepatic metastasis. This study investigated whether extended resections for advanced malignant pancreatic endocrine tumours influenced disease-free and disease-specific survival. Patients who had curative resection of pancreatic endocrine tumours were analysed retrospectively for disease-free and disease-specific survival, with a focus on the role of extended surgical resection. Forty-one patients were included in the analysis, 13 of whom underwent extended surgical resection in addition to pancreatic resection. This included partial liver resection in nine patients, portal vein resection in three, partial gastric resection in five and liver transplantation in three patients. There were no deaths in hospital or within 30 days. Median follow-up was 40 (range 2-239) months. Thirty-five, 24 and 13 patients survived more than 1, 3 and 5 years respectively. Patients who underwent extended resection had similar diseasespecific survival to those who had pancreatic resection alone (hazard ratio (HR) 1.50, 95 percent confidence interval 0.35 to 6.35) but with a higher frequency of complications (odds ratio 4.28). Among patients with liver metastases, the mortality rate was higher in those in whom liver resection was not possible than in patients who had liver resection (HR 9.24). Patients who had liver resection had similar disease-specific survival to those without liver metastases (HR 0.84). It was concluded that extended surgical resection for locally advanced and metastatic pancreatic endocrine tumours is feasible with encouraging diseasespecific survival [627].

CHILDREN

Diagnostics

Pancreatic autoantibodies

Significance of pancreatic autoantibodies determined by using exocrine pancreas (PAB) and recombinant pancreas antigens (rPAB), as well as importance of autoantibodies against goblet cells (GAB) are not known in pediatric patients with inflammatory bowel disease (IBD). Our aim was to determine the complex analysis of PAB, rPAB, GAB, antibodies against Saccharomyces cerevisiae (ASCA), and perinuclear components of neutrophils (pANCA) in pediatric IBD patients. Moreover, association with NOD2/CARD15 and disease phenotype was determined. 152 pediatric patients (median age 14 years) with IBD - 103 patients with Crohn's disease (CD) and 49 patients with ulcerative colitis (UC) - and 104 controls were included. Serum autoantibodies were determined by indirect immunofluorescens assay. NOD2/CARD15 variants were tested by polymerase chain reaction/restriction fragment length polymorphism. The presence of PAB and rPAB was significantly higher in CD (34 % and 36 %) and in UC (20 % and 25 %) compared to pediatric control cohort (0 % and 0 %). In addition, GAB positivity was significantly increased in patients with UC in comparison to CD and controls, respectively (UC 12 %, CD 2 %, controls 2 %). Specificity of PAB and rPAB was 100 percent, however, sensitivity was low. The combination of PAB and/or ASCA/pANCA improved the sensitivity of serological markers in CD (87 %) and in UC (80 %); specificities were 89 percent and 93 percent, respectively. Pancreatic autoantibodies (PAB, rPAB) and GAB were not related to clinical presentation, medical therapy or need for surgery in CD or in UC. In conclusion, pancreatic autoantibodies and GAB were specific for IBD but the sensitivity was limited as well as there was lack of correlation with clinical phenotype. Combinations of these antibodies have shown increased sensitivity, therefore, it may be recommended in the diagnostic procedure of IBD [628].

Acute pancreatitis

Acute pancreatitis in children is mostly due to abdominal trauma, diseases or congenital anomalies of the biliary-pancreatic tree. Both exogenous and endogenous functions of the gland could be disturbed by various levels of damage. Acute abdominal pain, gastrointestinal signs and general deterioration are the main clinical findings. The examination can be completed by blood and urine tests of amylase, electrolytes level, and the C-reactive protein. In addition to these tests, ultrasound, computed tomography and endoscopy are required as well. The therapy of choice is non-operative treatment using medicaments to control the pain, decrease the pancreatic activity and prevent further complications. If the conservative treatment fails, the surgical approach is necessary: drainage, resections, by-pass procedures, etc. It was concluded that acute pancreatitis is a very serious disease in childhood. Clinical experience and rational approach are very important in the diagnostic and therapeutic methods [629].

Laparoscopic necrosectomy

Acute pancreatitis (AP) in children usually follows a mild course but occasionally may be severally problematic. It was reported the case of a 12-year-old boy with severe AP who was managed with repeated laparoscopic pancreatic necrosectomy. Three weeks later he represented with a pancreatic pseudocyst that was treated with endoscopic gastrocystotomy. His abdominal pain persisted and a subsequent magnetic resonance cholangiopancreato-gram showed multiple gallbladder and common bile duct (CBD) stones that were missed on

previous imaging investigations. He underwent laparoscopic cholecystectomy with transcystic exploration of the CBD. The patient is currently well, more than 2 years following the definitive corrective surgery. This is the first case of laparoscopic pancreatic necrosectomy in a child [630].

Chronic pancreatitis

Etiology

Pancreatitis is an inflammatory disorder of the pancreas that can be acute or chronic. Acute pancreatitis is an "event" whereas chronic pancreatitis is a "process". Acute pancreatitis occurs suddenly and resolves without significant irreversible damage to the gland. Chronic pancreatitis (CP) can be considered the result of repeated acute inflammatory events of varying duration. The long-standing inflammatory injuries produce chronic inflammatory infiltrates, loss of normal pancreatic cells and fibrosis. In children, environmental factors seem to play a smaller role in the etiology of chronic pancreatitis than found in adults. A large percentage of children with CP are still considered to have idiopathic disease. A significant fraction has congenital anomalies of the biliary tree, pancreas, stomach, or duodenum. More than half of children with CP have mutations in the genes encoding the cystic fibrosis transmembrane conductance regulator (CFTR), cationic trypsinogen (PRSS1) or serine protease inhibitor Kazal type 1 (SPINK1). Mutations in CFTR and SPINK1 produce sporadic disease, whereas mutations in PRSS1 result in autosomal dominant hereditary pancreatitis. Mutations in SPINK1 increase the risk of chronic pancreatitis, and are considered disease modifiers. Specific CFTR genotypes are significantly associated with pancreatitis but the pathogenesis is complex, and other genes likely modify the risk. For instance, the combination of mutations in CFTR and SPINK1 increases the risk of CP to around 900-fold, much higher than the risk of a mutation in either gene alone [129].

Octreotide treatment

It was reported on the experience with the use of octreotide as primary or adjunctive therapy in children with various gastrointestinal disorders. A pharmacy database identified patients who received octreotide for gastrointestinal diseases. Indications for octreotide use, dosing, effectiveness, and adverse events were evaluated by chart review. A total of 21 patients (12 males), aged 1 month to 13 years, were evaluated. Eleven received octreotide for massive gastrointestinal bleeding caused by portal hypertension-induced lesions (n=7), typhlitis (1), Meckel's diverticulum (1), and indefinite source (2). Blood transfusion requirements were reduced from 23 ± 9 mL/kg to 8 ± 15 mL/kg. Four patients with pancreatic pseudocyst and/or ascites received octreotide over 14 ± 6 days in 2 patients. In 3 children, pancreatic pseudocyst resolved in 12 ± 2 days and pancreatic ascites resolved in 7 days in 2. Three patients with chylothorax received octreotide for 14 ± 7 days with complete resolution in each. Two infants with chronic diarrhea received octreotide over 11 ± 4.2 months. Stool output decreased from 85 \pm 21 mL/kg/day to 28 \pm 18 mL/kg/day, 3 months after initiation of octreotide. The child with dumping syndrome responded to octreotide in a week. Adverse events developed in 4 patients: Q-T interval prolongation and ventricular fibrillation, hyperglycemia, growth hormone deficiency, and hypertension. It was concluded that octreotide provides a valuable addition to the therapeutic armamentum of the pediatric gastroenterologist for a wide variety of disorders. Serious adverse events may occur and patients must be closely monitored [631].

Pancreatic solid tumors

Pancreatic tumors in childhood are rare. Standard therapeutic approaches are lacking. Our aim was to analyze treatment modalities and outcome in children with pancreatic tumors. Between 1980 and 2007, 55 patients with exocrine pancreatic tumors < 16 years old were registered. Data were obtained from the German Pediatric Tumour Registry. Medical records were evaluated and patient data were pseudonymized. Patient records of 29 children were available (9 male, 20 female, median age 11 years, range 3-16). In 18 patients a solidpseudopapillary tumor (SPT) was diagnosed, in 7 patients a pancreatic carcinoma (P-CA) (5 acinar cell carcinoma (ACC). 2 ductal adenocarcinoma (DCA)), and in 4 patients a pancreatoblastoma (PBL). In 69 percent of the patients the initial radiological findings led to an incorrect tentative diagnosis. Initial histopathological diagnoses were differing from the reference pathology in 50 percent of the SPT and 45 percent of the P-CA. In the group of SPT survival rate was 100 percent; all patients underwent surgical resection. There were two cases of tumor relapse and one late secondary malignancy of the pancreas (DCA). In P-CA patients, survival rate was 14%, in the PBL group the survival rate was 25 percent. Concepts of chemotherapy, radiotherapy, and surgical intervention in P-CA and PBL were varying widely. It was concluded that in all cases of pediatric PT reference pathology and reference radiology should be involved. Standardized treatment concepts as well as prospective data registrations need to be entrenched [632]

Pancreatoblastoma

Pancreatoblastoma is a very rare childhood tumor originating from the epithelial exocrine cells of the pancreas. It is the most common malignant pancreatic tumor in young children and has a mean age of diagnosis of 5 years. It is slow growing and its presentation is varied and often non-specific. Tumors tend to be quite large and appropriate cross sectional imaging is very important to assess for extent, metastatic disease, and resectability. Biopsy for tissue diagnosis is essential. Complete surgical resection is the goal of therapy although many patients are unresectable at initial diagnosis and require neoadjuvant chemotherapy. Adjuvant chemotherapy is also recommended and chemotherapeutic regimens involve cisplatin and doxorubicin. Even with curative resections, these lesions have a high recurrence rate and patients must be followed closely. Knowledge of this rare tumor is important for the clinician confronted with a large retroperitoneal mass in a young child [633].

In newborns

Pancreatoblastoma is a rare malignant tumor of the pancreas mostly diagnosed in childhood. The clinical presentation and outcome of infantile and congenital pancreatoblastoma have not been clearly elucidated. One report described recent experience with an unusual case of congenital pancreatoblastoma. Review of the scientific literature identifies approximately 200 cases of pancreatoblastoma. It was described the 9 infantile (aged 3 months or younger) and 4 congenital cases previously reported and summarize their clinical presentation and outcome. It was also defined the close association of infantile/congenital pancreatoblastoma and Beckwith-Wiedemann syndrome (50 %) versus all affected age groups (5 %) [634].

Pancreatic cystic tumors

The aim of one study was to assess the diagnosis and management of solid pancreatic neoplasm in children and the type of surgical treatment, focusing on short- and long-term outcomes. It was retrospectively reviewed the charts of all children who had undergone pancreatic resection for suspicion of pancreatic tumor between 1986 and 2008. It was studied the symptoms at diagnosis, the type of surgery, and the short- and long-term morbidity and mortality. Of 18 patients identified, there were 7 pseudopapillary tumors, 3

neuroblastomas, 2 rhabdomyosarcomas, 1 acinar cell carcinoma, 1 endocrine cell carcinoma, 1 renal angiomyolipoma, and 3 pancreatic cysts. Symptoms at diagnosis were abdominal trauma, abdominal mass, and jaundice. Operative procedures were duodenopancreatectomy (11), mid-pancreatic resections (2), splenopancreatectomy (2), distal pancreatectomy (1), and tumorectomy (2). There were no deaths related to surgery. The postoperative morbidity rate was 45 percent, including 2 cases of fistula (11 %) occurring after a mid-pancreatic resection and a pancreaticoduodenectomy. The median follow-up was 4 years (range 2-11). There was no diabetes mellitus, but there was 1 case of fat diet intolerance requiring pancreatic enzyme substitution. All of the children had a growth curve within normal limits. In this experience, pancreatic resections have proven to be a safe and efficient procedure, with low long-term morbidity, for the treatment of tumoral and selected nontumoral pancreatic masses [635].

Primary pancreatic lymphoma

Primary pancreatic lymphoma (PPL) is an extremely rare disease which occurs in pancreas, accounts for less than 1 percent of extra-nodal malignant lymphomas and 0.5 percent of cases of pancreatic masses. It was reported a case of PPL in a 15 year-old boy suffering from maturity onset diabetes of the young type 3 (MODY3) diagnosed at the age of 1 year [636].

Pancreatic pseudocysts

To review the use of endoscopic cyst gastrostomy (E-CG) as a treatment option for pancreatic pseudocysts referred to a tertiary paediatric surgical centre a retrospective review over a 10 year period (2001-2010) was performed. Cystgastrostomies were performed using 1 or 2 double pigtailed Zimmon stents (7-10 Fr) under general anaesthesia. Data are quoted as median (range). E-CG were performed in 7 (5 males) children (median age at presentation 12 years). Pancreatic pseudocysts were caused by acute pancreatitis in five (gallstones n=1, hereditary pancreatitis n=1, pancreatic divisum n=1, asparaginaseinduced n=1 and idiopathic n=1) and pancreatic trauma in two (motor vehicle accident n=1, and handlebar injury n=1). All cases were associated with a rise in serum amylase level, median 1028 (276-2077) IU/L at the peak of symptoms. Three children had pancreatic duct stent placement during ERCP as the initial therapeutic intervention, but went on to have E-CG later. One who had a huge pseudocyst at presentation had already undergone an open cyst gastrostomy which had recurred at 1 month. Rescue E-CG was performed 38 days later. All stents were removed endoscopically at 8 (6-40) weeks.E-CG was uncomplicated and pseudocysts resolved completely in five. One required repeat placement at 15 days due to catheter slippage with later full resolution. One child required open cystgastrostomy due to reaccumulation two months following removal of the stent. Median hospital stay post E-CG was 3 (1-23) days. There has been no recurrence at median follow-up of 18 (5-108) months. It was concluded that endoscopic cyst gastrostomy is a safe and effective alternative for the management of pancreatic pseudocysts in children and should now be considered as treatment of choice [637].

Minimally invasive surgical techniques are becoming increasingly popular within the pediatric population. Flexible endoscopy may enhance or replace existing techniques in the future. Many of the reported benefits of laparoscopy and thoracoscopy may apply to endoscopy and endoscopy-assisted procedures; however, no reports exist as to the application, results, and outcomes for these procedures in children. It was hypothesized that endoscopy is a useful and safe adjunct for pediatric surgical patients. Retrospective review of medical records for

patients who underwent endoscopy or endoscopy-assisted operations at two children's hospitals over 3 years (2007- 2010) was completed. During this time period, 30 procedures were performed on 28 patients. Indications for procedure, age, operative technique, operative times, surgical outcomes, complications, and length of stay for each patient were reviewed. Patient age ranged from 3 days to 20 years. Indications for operation included esophageal pathology (13), gastroduodenal pathology (14), pancreatic pseudocyst (2), and displaced sigmoid Chait® (Cook, Inc., Bloomington, IN, USA) tube. Although endoscopy was intended only as an adjunct in all cases, the planned procedure was satisfactorily completed with a purely endoscopic approach in six cases. There were no intraoperative complications, and minor postoperative complications including one stricture requiring dilation, postoperative stridor, and esophageal leak, were each successfully managed conservatively. Endoscopy offers a promising adjunct to more traditional minimally invasive techniques in children. In some cases, endoscopy may offer an alternative to more invasive procedures or eliminate the need for tube thoracostomy or post-procedural contrast studies in some esophageal cases [638].

Pancreatic aneurysms

Splenic artery pseudoaneurysms (SAPs) are rare in children and usually follow abdominal trauma. Although pancreatitis is a well-known cause for SAP in adults, pancreatitis resulting in SAP has only sporadically been reported in children. Before the refinements of endovascular techniques for management of SAP, surgery used to be the mainstay of treatment, often resulting in splenectomy. Recent technical advancements, including development of smaller delivery systems and microcatheters, have made endovascular treatment feasible in children with SAP and increased chances of splenic preservation. In one article, it was reported a rare case of SAP associated with a pancreatic pseudocyst in a 5-year-old boy with recurrent acute pancreatitis that was managed by endovascular stent graft and cystogastrostomy [639].

Trauma

Traumatic pancreatic transection is uncommon. The role of laparoscopy in the setting of this injury has not been well described. Six large-volume pediatric trauma centers contributed patients <18 years of age who underwent a distal pancreatectomy for traumatic pancreatic transection from 2000 to 2010. Results: Twenty-one patients without another indication for emergency laparotomy underwent a distal pancreatectomy for Grade III pancreatic injuries, of which 7 underwent laparoscopic distal pancreatectomy. Mean (\pm SD) age was 9 \pm 5 years, and 67 percent were male. There was no difference in the presence of other injuries between the two groups (43 % in each group). Computed tomography revealed a transected pancreas in 85 percent of the laparoscopic patients and 75 percent of the open group. Mean operative time was 218 \pm 101 minutes with laparoscopy compared with 195 \pm 111 minutes with the open procedure. Median duration of hospitalization was 6 days (range, 6-18 days) in the laparoscopic group compared with 11 days (range, 5-26 days) in the open group. Postoperative morbidity was not different between the two groups (57 % vs 21 % for laparoscopic vs open). It was concluded that laparoscopy is equivalent to open distal pancreatectomy in children with select traumatic pancreatic injuries [640].

Pancreatic trauma is more frequent in children than in adults and is often caused by trauma to the upper part of the abdomen. Mortality is low, but morbidity is high. Pancreatic trauma can be treated operatively or non-operatively, but there is disagreement about the optimal treatment strategy for patients with severe pancreatic lesions. In general, good results are

achieved with non-operative treatment and secondary surgery is avoided, but prospective trials are needed to evaluate the method [641].

Treatment of blunt injury of the pancreas in children remains controversial. Some prefer nonsurgical treatment, whereas others prefer surgical management in selected cases. This report reviews our management strategies of children with blunt pancreatic trauma and their outcomes. Medical records of 7 children with traumatic pancreatic injury were retrospectively analyzed in our institutions. In addition, we reviewed the pertinent literature. There were 2 males and 5 females with a median age of 8 years. Pancreatic injury was classified in 3 patients as grade I, in 2 patients as grade II, and in 2 patients as grade III (AAST). The two grade III children underwent ERCP preoperatively. ERCP showed injury to the main pancreatic duct in both of these patients, and emergency surgery was performed for both of them. These operative methods were spleen-preserving distal pancreatectomy and only drainage at the margin of the pancreas with non-resection, respectively. All 7 cases survived. It was concluded that ERCP is helpful for the diagnosis of suspected cases in pancreatic injury with grade III. In hemorrhagic shock state, appropriate surgical procedures with only drainage at the margin of the pancreas are useful for the treatment of pancreatic fistula in children [642].

Seat-belt trauma

A short cut review was carried out to establish whether the seat belt sign was a significant predictor of intra-abdominal injury in children involved in motor vehicle collisions. 51 papers were found using the reported searches, of which three presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. It is concluded that seatbelt sign appears to be associated with an increased risk of intra-abdominal injuries, especially gastrointestinal and pancreatic injuries [643].

PSEUDOCYSTS AND PSEUDOANAEURYSMS

Overview of pseudocysts

Pancreatic pseudocysts are fluid collections arising from leakage of the pancreatic duct lacking an epithelial lining. They usually occur following the course of an acute pancreatitis, chronic pancreatitis or secondary to an abdominal trauma. The incidence of pseudocysts in the phase of an acute pancreatitis is 5 percent to 16 percent whereas the incidence in chronic pancreatitis is higher with percentages varying from 20 to 40 percent. Radiologic imaging of pseudocysts frequently shows a single cystic lesion, without septations or solid components. Aspirated fluid often has a low viscosity, high amylase, and cytology which is consistent with an inflammatory origin. The cysts are often filled with protease-free serous fluid if no connection to the pancreatic duct exists. Whereas size of >6 cm and duration of more than 6 weeks used to be main indicators for intervention, currently symptomatology is the main indicator for intervention [517].

Pancreatic pseudocyst develops in both acute and chronic pancreatitis. It is an entity likely to either remain asymptomatic or develop devastating complications. Despite being diagnosed easily, treatment exercise is still at crossroads whether in the form of internal or external drainage or endoscopic, laparoscopic, or open intervention with a good radiological guidance. The first description of pseudopancreatic cyst dates back almost two and half centuries to 1761 A.D. by Cannon et al. The management of cystic changes of the pancreas is an old problem. Eugene Opie, at the beginning of twentieth century, was the first to distinguish true pancreatic cysts, which are, by definition, lined by epithelium, from pseudocysts, which are surrounded by a wall composed of collagen and granulation tissue. More than two centuries after the first description, some clear consensus and guidelines were evolved in the Atlanta classification of 1993. The Atlanta classification consists of four distinct disease entities: acute fluid collections that develop early in the course of acute pancreatitis and do not yet have a cyst wall; acute pancreatic pseudocysts, which arise as sequelae of acute pancreatitis or trauma, and whose wall consists of granulation tissue and extracellular matrix; chronic pancreatic pseudocysts, which arise as sequelae of chronic pancreatitis and are likewise surrounded by a wall: pancreatic abscesses, which are intraabdominal collections of pus immediately adjacent to the pancreas, without any large areas of necrosis. Acute fluid collections, pancreatic pseudocysts, and pancreatic abscesses can be distinguished from one another by the history, imaging studies of the wall of the abnormality and its contents, and, if necessary, a needle aspiration of the content. Pseudocysts are formed after acute as well as chronic pancreatitis but more common after acute exacerbations of chronic pancreatitis than acute pancreatitis. There is lack of data containing randomized case-control studies, but numerous case series and reports indicate that pancreatic injury leads to pseudocyst formation. Pancreatic pseudocysts often arise as a complication of acute or chronic pancreatitis. The prevalence of pancreatic pseudocysts in acute pancreatitis has been reported to range from 6 to 19 percent. The prevalence of pancreatic pseudocysts in chronic pancreatitis range 20 to 40 percent. Pancreatic pseudocysts most commonly arise in patients with alcoholic chronic pancreatitis (from 70 % to 78 %). The second most common cause is idiopathic chronic pancreatitis (from 6 % to 16 %), followed by biliary pancreatitis (from 6 % to 8 %). The incidence of pseudocyst is low ranging from 0.5 to 1 per 100000 adults per year. D'Egidio and Schein, in 1991, described a classification of pancreatic pseudocyst based on the underlying etiology of pancreatitis (acute or chronic), the pancreatic ductal anatomy, and the presence of communication between the cvst and the pancreatic duct and defined three distinct types of pseudocvsts [9]. Typel, or acute "postnecrotic" pseudocysts that occur after an episode of acute pancreatitis and are associated with normal duct anatomy, rarely communicates with the pancreatic duct. Type II, also postnecrotic pseudocysts, which occurs after an episode of acute-on-chronic pancreatitis (the pancreatic duct is diseased but not strictured, and there is often a ductpseudocyst communication). Type III, defined as "retention" pseudocysts, occurs with chronic pancreatitis and is uniformly associated with duct stricture and pseudocyst duct communication. Another classification, based entirely on pancreatic duct anatomy, is proposed by Nealon and Walser:

- Type I: normal duct/no communication with the cyst
- Type II: normal duct with duct-cyst communication
- Type III: otherwise normal duct with stricture and no duct-cyst communication
- Type IV: otherwise normal duct with stricture and duct-cyst communication
- Type V: otherwise normal duct with complete cutoff
- Type VI: chronic pancreatitis and no duct-cyst communication
- Type VII: chronic pancreatitis with duct-cyst communication

Pseudocyst of pancreas must be preceded by attacks of pancreatitis in either acute or chronic form. Most of the times, clinical, biochemical, and radiological evidence of pancreatitis present, but still a large number of patients may present with features of pancreatic pseudocyst without any documentary evidence of pancreatitis. One should always consider the possibility of a pseudocyst in a patient who has persistent abdominal pain, anorexia, or abdominal mass after a case of pancreatitis. Rarely, patients present with jaundice or sepsis from an infected pseudocyst. In patients presenting with pancreatic cyst incidentally discovered on imaging, a crucial point is to define whether the patient has had prior history of pancreatitis. Rarely, patients with large pancreatic pseudocyst may be asymptomatic occasionally. Tender abdomen with palpable mass is the positive finding on physical examination. Fever, icterus, and pleural effusion may be present in complicated pseudocyst. If pseudocyst ruptures then features of secondary peritonitis set in and presentation may be like septicaemic shock. The diagnosis of a pancreatic pseudocyst is usually established by imaging studies, among which transabdominal ultrasonography is important as an initial investigation. Computerized tomography (CT) is often the imaging method of choice, with 82 to 100 percent sensitivity and 98 percent specificity [644].

Biochemical parameters have limited role in diagnosis. Among remarkable parameters are serum amylase and serum lipase, which will be elevated in most cases. Liver functions are normally unchanged but may be deranged in cases where obstruction to the biliary tract occurs. Another thing to be considered is strong possibility of biliary peritonitis if liver parameters deranged. Other inflammatory marker C-reactive protein is raised and is of prognostic significance only. Elevated triglycerides and low serum calcium are indirect indictors of panreatic pseudocyst. Differential diagnosis of pancreatic pseudocyst always may be of two possibilities either intrapancreatic lesions or extrapancreatic lesions. Intrapancreatic diseases mimicking pancreatitis are:

- pancreatitis (acute and chronic)
- pancreatic necrosis
- pancreatic abscess
- adenocarcinoma of pancreas
- cystic neoplasm of pancreas
- pancreatic artery pseudoaneurysm

Extrapancreatic diseases mimicking pancreatitis are:

- peptic ulcer disease
- acute cholecystitis and cholelithiasis
- gastric cancer
- abdominal aortic aneurysm
- ovarian cysts and carcinoma
- acute myocardial infarction

- pneumonia
- intestinal obstruction
- intestinal ischemia.

Among different imaging modalities, ultrasound (US) is the foremost diagnostic tool and also useful pointer of diagnosis in most of the cases. It may be used as:

- transabdominal US
- colour doppler study
- duplex scanning
- endoscopic USG.

Pancreatic pseudocyst appears as anechoic structure usually round or oval and surrounded by a smooth wall associated with distal acoustic enhancement on US examination. They are well defined and round or oval, and they are contained within a smooth wall. During the early phases of their development, pseudocysts can appear more complex, with varying degrees of internal echoes. If the earliest detection missed sometimes it may be due to excessive bowel gas. When necrotic debris or hemorrhage presents inside cyst or infection sets in then the interpretation on USG may be difficult. Color Doppler or duplex scanning should always be performed in cystic lesions to ensure that the lesion in question is not a giant pseudoaneurysm. Sensitivity rates for US in the detection of pancreatic pseudocysts are from 75 to 90 percent. Therefore, US is inferior to CT, which has a sensitivity rate of 90 to 100 percent. Endoscopic ultrasound (EUS) is a test of choice to differentiate between cystic neoplasms of pancreas from pseudocyst. EUS is usually used as a secondary test to further evaluate pancreatic cyst detected by other imaging modality (US, CT or MRI). For the distinction of acute fluid collections from pancreatic abscesses and acute pancreatic pseudocysts, endosonography (EUS) has the highest sensitivity (93 to 100 %) and specificity (92 % to 98 %). The diagnostic puncture of a pseudocyst under EUS guidance helps distinguish cystic malignancies from pseudocysts. A malignant lesion is more likely present when the carcinoembryogenic antigen (CEA) value exceeds 192 ng/mL and when the cyst contents are highly viscous. Visualization of the pancreas via EUS provides high quality images due to the close proximity analysis, which are helpful to detect malignancy. An elevated CEA level on FNAC within the cyst fluid strongly suggests mucinous lesion. Amylase levels are usually high in pseudocysts and low in serous cystadenoma of the ultrasound transducer to the area of interest. Criteria suggestive of cystic neoplasm include a cyst wall thickness of greater than 3 mm, macroseptation (all cystic components more than 10 mm), the presence of a mass or nodule, and cystic dilation of the main pancreatic duct. Aspiration of cyst fluid under EUS guidance and biochemical analysis with molecular analysis helps in differentiating different cystic neoplasms of pancreas. Mutational changes and DNA content point towards malignancy [644]

US has several limitations, as compared with CT, in the initial diagnosis of a pseudocyst: the presence of overlying bowel gas decreases the sensitivity of US, and unlike CT, US examinations are highly operator dependent. A thick-walled, rounded, and fluid-filled mass adjacent to the pancreas on an abdominal CT scan in a patient with a history of acute or chronic pancreatitis is virtually pathognomonic for pancreatic pseudocyst. In acute manifestations when ileus or excessive gas shadow or bowel obstruction is a problem in US evaluation, CT scan is definitely better and is purposeful in diagnosing pseudocyst. It is almost diagnostic and no other supplementary investigation that is required to confirm the diagnosis. Major advantage of CT scan is the detection of an objective and detailed anatomy as well as pathology. In addition to pancreas, extrapancreatic pathology as well as status of adjoining organs, for example, gallbladder, liver, common bile duct, stomach, and duodenum can be perfectly assessed. Contrast-enhanced CT is now the primary tool of investigation for initial diagnosis of pancreatic pseudocysts. USG should be done for the follow-up of asymptomatic pseudocysts or when diagnosis is uncertain. The only major limitation of CT

scan is that it is unable to differentiate cystic neoplasm of pancreas from pseudocyst, and the main pathology to be missed is mucinous cystadenomas and intraductal papillary mucinous cystadenoma (IPMN) [644].

MRI and MRCP are accurate and sensitive diagnostic aids for defining the anatomy of duct better than any other diagnostic tool. But these are not used routinely as adequate information is obtained in maximum cases by CT, and very rarely ductal anatomy is needed to be calibrated with too much precision and MRI/MRCP is required. Pancreatic duct and biliary system are best visualized in detail although interpretation of integrity of pancreatic duct may be difficult. MRCP techniques can also depict subtle branch-chain dilatation in chronic pancreatitis. MRI is also highly sensitive to the detection of bleeding with complex fluid collections. The role of endoscopic retrograde cholangiopancreatography (ERCP) is limited to some extent for therapeutic intervention rather than diagnostic purpose. It may help in planning an intervention after the increased use of endoscopic USG its role is gradually decreasing [644].

Most pseudocysts resolve with supportive medical care. Of 114 patients with the diagnosis of pancreatic pseudocyst followed over a period of 5 years 46 patients underwent primary operative therapy, with 13 percent undergoing emergency operations for pseudocyst-related complications. Morbidity occurred in 26 percent of patients (emergency operations, 67 %; elective procedures, 10 %) without any mortality. The remaining 68 patients were initially treated with a nonoperative expectant approach. Severe and life-threatening complications in this group (followup for a mean of 46 month) occurred in only six patients (9 %); 19 patients eventually underwent elective operations directed at either the pseudocyst or other complications related to pancreatitis. Overall, in patients managed by a nonoperative approach, resolution of the pseudocyst occurred in 57 percent of the 24 patients with satisfactory radiographic follow-up, with 38 percent resolving more than 6 months after diagnosis. Although patients eventually undergoing operation tended to have larger pancreatic pseudocysts than the patients managed successfully nonoperatively (6.9 cm versus 4.9 cm), no serious complications occurred in seven patients with pancreatic pseudocysts greater than 10 cm who were treated expectantly. Large-sized and longstanding cysts are not likely to respond on conservative treatment and more likely to have complications during the course of the disease. Morbidity and mortality are more commonly found in this group. These patients need surgical intervention and usually managed surgically. But some studies say that size and duration never matter, and actually these patients too have excellent surgical results and do well. There are two definite conclusions that the presence and the severity of symptoms and complications are determinants of prognosis and course in pancreatitis [644].

Most of the symptomatic and complicated pancreatic pseudocysts need intervention in any form during the course of the disease. Intervention options are either guided endoscopically, radiologically, laparoscopically, or open/direct. To date, no prospective controlled studies have compared directly percutaneous, surgical, and endoscopic drainage approaches. As a result, the management varies based on local expertise, but in general endoscopic drainage is becoming the preferred approach followed by laparoscopic approach. There is no consensus regarding methods of intervention in pancreatic pseudocyst although there is no controversy with conservative treatment. Minimal intervention with maximal conservative approach remains the most widely acceptable option of therapeutic intervention in pancreatic pseudocyst. Small sized asymptomatic cysts need no intervention at all. Asymptomatic largesized cyst should be intervened after six weeks only and in the meantime is must be under close monitoring to detect the earliest symptoms or complications. Only in symptomatic cases or if any complication develops, intervention is required before six weeks. Cyst of any size should be intervened once it becomes symptomatic or if complications develop irrespective of duration, size, or site. So two things are important determinants the regarding plan of management: size when it is more than five cm and duration when it is more that six

weeks. External drainage can be achieved radiologically by using CT or US guidance. In this technique, a drainage pigtail catheter is placed percutaneously into the fluid cavity, and the fluid is drained. Three-dimensional ultrasonography has been reported useful for the guidance of catheters into cyst cavities and avoiding vessels. When the drainage output becomes minimal, the catheter is removed. Contrast injection into the cyst cavity will demonstrate the size of the remaining cavity, and this finding can be used to monitor the progress. This technique is successful in resolving pseudocysts, but it has a high risk of infections. This technique is definitely a failure if the catheter tends to block repeatedly. It tends to create significant discomfort to the patient. Furthermore, the catheter tends to clog and may require repositioning and exchange. The reported long-term success rate of pseudocyst resolution for US-guided pseudocyst drainage is around 50 percent. Unsuccessful drainages are usually caused by large ductal leaks or obstruction of the main pancreatic duct. Percutaneous catheter drainage is contraindicated in patients who are poorly compliant and cannot manage a catheter at home. It is also contraindicated in patients with strictures of the main pancreatic duct and in patients with cysts containing bloody or solid material. In cases of failure of external percutaneous drainage radiologically, this approach is applied either by open method or by laparoscopy. It can be a good option for the patients who cannot tolerate endoscopic drainage. Stoma is created between the most dependent part of the cyst and the adjoining stomach, jejunum, or ileum to provide effective drainage. For surgical drainage, either laparoscopic or open method can be opted as both are effective for relief, but laparoscopic approach definitely carries low morbidity and mortality as compared to open techniques. Surgical drainage, which is increasingly done laparoscopically with a cholecystectomy if needed is the preferred mode then open approach. External drainage of pseudocyst should only be carried out in case of emergency relief of severe symptoms and sepsis. Otherwise, EUS or surgical drainage are the procedures of choice. Blind external drainage when duct status is unsure results in difficultto-manage pancreatic fistulae [644].

Endoscopic drainage of pseudocysts is becoming the preferred therapeutic approach because it is less invasive than surgery. The intervention done is minimal and avoids the need for external drain and has a high long-term success rate. Internal drainage is accomplished with either a transpapillary approach with ERCP or direct drainage across the stomach or duodenal wall. A transpapillary approach is preferable when the pseudocyst communicates with the main pancreatic duct, usually in the gene of the pancreatic duct. This approach is also successful for patients with pancreatic duct disruption. The endoscopic approach is guided by the presence of a bulge into the lumen of the stomach or duodenum in order to determine the entry site for catheterization. This approach has several inherent risks. including missing the pseudocyst, injuring intervening vessels, and suboptimal placement of the drainage catheter. Therapeutic echoendoscopes now make it possible to treat pseudocysts with EUS-guided transmural stenting. Several series have described the deployment of a 7 Fr stent that is introduced with a needle-knife catheter. A new largechannel echoendoscope allows the use of 10 Fr stent across the stomach or duodenum. In a large retrospective analysis of 603 patients who were undergoing EUS-FNA of pancreatic cysts, possible infection developed in only a single patient. The majority of patients in this series (90 %) received antibiotic prophylaxis, most commonly a fluoroquinolone given for 3 days after the procedure, and this may possibly explain the low infection rate. The benefit of prophylactic antibiotics before an FNA of cystic lesions has not been evaluated by prospective randomized studies. The ASGE, in 2008, published the guidelines for prophylactic use of antibiotics for GI endoscopy. According to these guidelines, prophylaxis with an antibiotic, such as a fluoroquinolone, is administered before EUS-FNA of cystic lesions along the GI tract including pancreatic cyst. Antibiotics may be continued for 3-5 days after the procedure (supported by observational studies). The administration of antibiotic prophylax, a fluoroquinolone administered before the procedure and continued for 3 days after the procedure, is a reasonable regimen. Final decision on EUS versus surgical drainage is important and interesting as the decision making depends upon the profile of the

patient. It is important to know that multiple procedures are sometimes necessary to ensure adequate drainage. Also when there is a large amount of solid debris, EUS drainage does not give good results. There has been significant technical advancement in EUS-guided drainage procedures with improved equipments and skill base. It is certain that EUS drainage will be more and more a preferred option over surgical drainage in the future too [644].

Pancreatic pseudocyst needs close followup to early detect the most dreadful complications, which may be devastating if it remain unrecognized for long.

- Infection: infection occurs either spontaneously or after therapeutic or diagnostic manipulations. While infected pseudocyst can initially be treated with conservative means, a majority of patients will require intervention. Traditionally, surgery has been the preferred modality but endoscopic treatment is gaining acceptance. An external drainage may be necessary in selected situations such as when there is evidence of gross sepsis and the patient is too unstable to undergo surgical or endoscopic drainage
- *Hemorrhage*: hemorrhage can greatly complicate the course of a pseudocyst and can be devastating. The morbidity and mortality is very high because it can appear without warning and is usually due to erosion of a major vessel in the vicinity of the pseudocyst. If not recognized immediately, life of the patient may be jeopardized. Interventional radiology can play an invaluable role both in locating the source of bleeding and in embolisation of the bleeding vessel. Without prior information of the bleeding point, surgical exploration can be hazardous and challenging.
- Splenic infarction and thrombosis: complications of pseudocyst include massive hemorrhage into the pseudocyst, sepsis with splenic infarction, and splenic vein thrombosis. The diagnosis of intrasplenic pseudocyst, based on clinical findings alone, is difficult to arrive at but should be suggested by the presence of a mass in the left upper quadrant. Sonography and computerized axial tomography may be particularly helpful in confirming splenic involvement. Selective celiac arteriography should be performed whenever splenic involvement is suggested in order to confirm the diagnosis and to search for pseudoaneurysm formation. Urgent surgical intervention is usually warranted in view of the high incidence of serious complications and the propensity toward rapid clinical deterioration. Resection of the pseudocyst by splenectomy and distal pancreatectomy is the treatment of choice
- Rupture: rupture of a pseudocyst can have either a favorable or an unfavorable outcome, and this depends on whether it ruptures into the gastrointestinal tract, into the general peritoneal cavity, or into the vascular system. Rupture into the gastrointestinal tract either results in no symptoms or leads to melaena or hematemesis that usually requires urgent measures. Rupture into the general peritoneal cavity results in features of peritonitis and occasionally hemorrhagic shock. Emergent surgical exploration is usually required. While an internal drainage should always be aimed for, usually a thorough abdominal lavage and external drainage are all that can be achieved safely
- *Biliary complications*: biliary complications occur due to a large cyst in the pancreatic head region obstructing the common bile duct and resulting in obstructive jaundice. Therapeutic endoscopy with short-term biliary stenting is valuable in this situation. It can be retained until either the pseudocyst resolves or is treated by intervention
- *Portal hypertension*: portal hypertension can result from compression or obstruction of the splenic vein/portal vein either by the cyst alone or by the cyst in conjunction with underlying chronic pancreatitis. In this situation, surgery appears to be the only

treatment modality available, and an appropriate surgical procedure can effectively treat this form of portal hypertension

- *Gastric outlet obstruction*: pseudocysts around the head of the pancreas are likely to cause gastric outlet obstruction. Once the features of gastric outlet obstruction develop, it needs certainly intervention and decompression or drainage of the cyst.

Pseudocysts after acute pancreatitis

The aim of one study was to analyze the incidence, risk factors, and clinical outcomes of pancreatic pseudocyst after acute or acute-on-chronic pancreatitis. It was retrospectively reviewed the medical records of 350 patients with acute pancreatitis and 55 patients with acute-on-chronic pancreatitis. Pancreatic pseudocyst developed in 15 percent of acute pancreatitis and in 42 percent of acute-on-chronic pancreatitis. In the acute-on-chronic pancreatitis group, interval from symptom onset to hospital visit was longer, and the incidence of recurrent pancreatitis and alcoholic etiology was higher than that of the acute pancreatitis group. There was no significant difference in the spontaneous resolution rate between both groups. Of the total 68 conservatively treated patients with pseudocyst, the pseudocyst decreased in size or disappeared in 78 percent and showed no change in 2 percent. The risk factors of pseudocyst were the presence of underlying chronic pancreatitis, the interval from symptom onset to visiting the hospital, and an alcoholic etiology. The factorpredicted spontaneous resolution was a single lesion. Thus, pseudocyst developed more frequently in patients with acute-on-chronic pancreatitis, and most pseudocysts improved spontaneously irrespective of underlying chronic pancreatitis. A longer period of a "wait-andsee" policy for more than 6 weeks is suggested for asymptomatic pseudocyst, especially for a single lesion [645].

Previous studies on the development of pancreatic pseudocysts following acute pancreatitis were monocentric, mostly retrospective, did not fulfil the Atlanta criteria, and featured a mixture of patients with post-acute and chronic pancreatitis. Therefore, the natural course of pancreatic pseudocysts after acute pancreatitis and the reasons for their spontaneous resolution remain unknown. One prospective study of 369 patients investigated the prognostic factors for development of pancreatic pseudocysts and for their spontaneous resolution after a first episode of acute pancreatitis. On discharge, 124 (34 %) patients still had pancreatic fluid collections. The prognostic factor for these fluid collections was severe acute pancreatitis. Follow-up examination 3 and 6 months later showed pancreatic pseudocysts in 36 (10 %) patients (30 with and 6 without prior fluid collection), and in 27 (7 %) patients (25 with and 2 without pancreatic pseudocyst after 3 months), respectively. The prognostic factors for their development were alcohol abuse and an initial severe course of the disease. Spontaneous complete resolution of the pancreatic pseudocysts occurred in 11 (31 %) of the 36 patients. Prognostic factors for the spontaneous resolution were no or mild symptoms (nausea, vomiting, abdominal pain) and a maximal cyst diameter of <4 cm. Patients with a first severe attack of acute pancreatitis and fluid collections at discharge should be checked by ultrasonography for pancreatic pseudocysts 3 months later. In patients with a small pseudocyst and mild symptoms therapy may be postponed for a further 3 months, since spontaneous resolution is possible [646].

Mediastinal pseudocyst

A 62-year-old man was admitted with dyspnea. Computed tomography (CT) revealed left massive pleural effusion and a cystic lesion in the posterior mediastinal compartment extending to the pancreatic head via the esophageal hiatus. The pleural effusion had a high

amylase content. Based on these findings, it was diagnosed mediastinal pancreatic pseudocyst accompanied by pancreatic pleural effusion. The patient was treated him with CT-guided puncture and endoscopic pancreatic drainage. Endoscopic pancreatic treatment is possible for pancreatic pseudocysts [647].

Splenic pseudocyst

Splenic pseudocyst is a rare disease associated with chronic and acute pancreatitis splenic pseudocyst is treated by distal pancreatectomy and splenectomy. A 47-year old woman with a 10-year history of alcohol abuse presented with epigastric and left upper quadrant pain of 3 days duration. Abdominal CT showed a 4.0×4.5 cm sized cystic lesion in the tail of the pancreas. Analgesics were administrated for the relief of abdominal pain. On the 4th hospital day, the patient complained more of left upper quadrant pain, so we took follow up CT scans. On follow up CT, one large splenic pseudocyst with size of 9.5×4.5×10.0 cm was noted. The patient was treated conservatively by percutaneous catheter drainage and discharged on the 13th hospital day. This case is the first case report of splenic pseudocyst treated conservatively, not by surgery in Korea [648].

Intramural duodenal pseudocyst

An intramural pseudocyst in the alimentary tract develops as a rare complication of acute pancreatitis or trauma. A 60-year-old woman with pancreatic head cancer underwent preoperative radiological examinations, which revealed a 45-mm cystic mass around the second portion of the duodenum. Endoscopic ultrasonography confirmed a cystic lesion in the submucosal layer of the duodenum and fine needle aspiration cytology of the cystic contents suggested adenocarcinoma. The cystic fluid was amylase-rich, at 17040 U/I. We performed pancreaticoduodenectomy for the pancreatic head cancer. Pancreatography of the resected specimen showed a communication between the main pancreatic duct and the cystic lesion. The cut surface of the resected specimen revealed a cystic lesion, which surrounded the duodenum. Pathologically, the cystic lesion was diagnosed as a pseudocyst, located between the dissociated smooth muscle layers of the duodenum [649].

Pseudocyst of the pancreas in a pregnant patient.

Gallstone pancreatitis is a rare problem in pregnant patients. A primigravida with persistent symptoms of abdomen pain, nausea, vomiting, and inability to tolerate oral diet presented at 5 weeks of pregnancy. A laparoscopic cystogastrostomy with cholecystectomy was performed at 13 weeks of pregnancy. There are only 10 case reports in literature of pseudocyst in pregnancy and in none of them ante partum surgical management was done [650].

EUS-guided scanning

Surgery for pancreatic pseudocysts (PPCs) may be associated with high rates of complication and mortality. Since its introduction in the late 1980s, endoscopic drainage of PPCs has become established as an alternative nonsurgical approach. The obvious limitation of this technique is its relatively blind approach. The ideal approach for PPC puncture combines endoscopy with real-time endosonography using an interventional echoendoscope. Endoscopic ultrasonographic longitudinal scanners can be used for

guidance of transmural punctures and drainage procedures, as well as to access a dilated pancreatic duct if the duct cannot be drained by conventional methods because of complete obstruction. In this chapter, we will review the indications, techniques and clinical algorithm for EUS-guided pseudocyst drainage and pancreaticogastrostomy [651].

Endoscopic treatment

Techniques of endoscopic pseudocyst management continue to evolve, but the principles of proper patient selection and careful consideration of the available therapeutic options remain unchanged. Endoscopic management is considered first-line therapy in the treatment of symptomatic pseudocysts. Clinicians should be vigilant in the evaluation of all peripancreatic fluid collections to exclude the presence of a pancreatic cystic neoplasm and avoid draining an immature collection. Expectant management with periodic observation should be considered for the minimally symptomatic patients, even after the traditional 6 weeks of maturation. Further, symptoms, complications, and expansion on serial imaging should prompt intervention by endoscopic, surgical, or percutaneous methods. Pseudocysts should only be punctured when the wall has had sufficient time to mature and after pseudoaneurysm has been ruled out by careful imaging. Small to moderately sized pseudocysts (< 4-6 cm) that communicate with the pancreatic duct are good candidates for endoscopic transpapillary stenting. For larger lesions requiring transmural drainage, EUS guidance is preferable, but good results can be achieved with ENL. EUS may be particularly useful in permitting drainage in patients with suspected perigastric varices or if an endoscopically visible bulge is not apparent. Necrosis is a significant factor for a worse outcome; aggressive debridement with nasocystic or percutaneous endoscopic gastrostomy-cystic catheter lavage plus manual endoscopic techniques for clearing debris should be used. Endoscopic failure, especially in cases with significant necrosis, should be managed operatively. Percutaneous drainage is a good option for immature infected pseudocysts or in patients who are not optimal candidates for other procedures. Close cooperation between endoscopists, surgeons, interventional radiologists, and other healthcare providers is paramount in successfully managing these patients [652].

EUS-guided

Tubular plastic and metal stents have inherent shortcomings when used for transenteric drainage of fluid collections. To evaluate a novel lumen-apposing, self-expandable metal stent for EUS-guided drainage of pancreatic pseudocysts and the gallbladder a study involved 15 patients (median age 54 years) with symptomatic pancreatic pseudocysts who underwent 12 transgastric and 3 transduodenal pseudocyst drainage procedures. Five patients (median age 70 years) with acute cholecystitis underwent 4 cholecystoduodenostomies and 1 cholecystogastostomy. The stents were deployed under EUS guidance, passage of an endoscope through the stent lumen for pseudocystoscopy or cholecystoscopy, transenteric endoscopy-guided interventions including biopsy. necrosectomy, and stone removal. All stents were successfully deployed without complication, with a median time to removal of 35 days. All pseudocysts resolved after a single drainage procedure. One stent migrated into the stomach, and the remaining 14 were found to be patent at the time of removal. There was no pseudocyst recurrence during the 11 month median follow-up period. One gallbladder stent remains indwelling and fully patent at 12 months. Resolution of acute cholecystitis was observed immediately after stent implantation. No recurrence of symptoms was observed during a median follow-up period of 9 months. It was concluded that transenteric drainage of pancreatic pseudocysts and the gallbladder by using a novel, lumen-apposing, metal stent was accomplished with high technical and clinical success in this pilot observational study [653].

The aim of one prospective study was to compare the feasibility, technical success rate and complication between single-step endo-ultrasonography (EUS)-guided and two-step EUS-guided drainage technique for symptomatic pancreatic pseudocyst. Twenty-one pancreatic pseudocyst patients with clear intra-cystic fluid that needed to be drained were divided into two groups, depending on the availability of the therapeutic echoendoscope at the time of the procedure: group 1 (13 patients) underwent a single-step EUS-guided endoscopic drainage and group 2 (8 patients) underwent a two-step EUS-guided drainage technique. In group 1 immediate technical success was achieved in 92 percent (12/13); two patients had recurrent pancreatic pseudocyst and both were successfully treated by a second EUS-guided drainage. Clinical success was achieved in all cases. In group 2 technical success was achieved in 75 percent of the patients (6/8). One patient (13 %) bled 36 h after the procedure. Five out of 6 patients had long-term success. Clinical success was significantly greater in group 1. It was concluded that the technique of single-step EUS-guided drainage was superior to the technique of a two-step EUS-guided drainage technique for pancreatic pseudocyst drainage [654].

Pancreatic pseudocysts arise as a complication to acute or chronic pancreatitis. Transmural drainage under guidance of endoscopic ultrasound (EUS) is a minimally invasive approach. The results of a case series was retrospectively reviewed with a mean follow-up of 441 days. Twenty-two consecutive patients (mean age 51 years, 13 men) who had undergone EUSguided drainage of pancreatic pseudocysts were included between 2005 and 2010. The mean cyst size was 8 cm. One or two 10 Fr. double pigtail stents were inserted into the pseudocvst from either the stomach or the duodenum. Insertion of a stent failed in three of 22 patients. Two cases were discontinued due to technical difficulties. One procedure was converted to a surgical cystogastrostomy. In 19 patients, a stent was successfully inserted. Three developed symptomatic recurrences due to stent malfunction. One developed a pseudocyst that mechanically obstructed the common bile duct. One developed a malignant cyst. One had a surgical cystogastrostomy for reasons unrelated to the stent insertion. For 13 patients (59 %), a single endoscopic treatment resulted in relief of symptoms and resolution of the pseudocysts. However, one of these subsequently developed an asymptomatic pseudocyst. EUS-guided endoscopy has only few severe complications and long-term results are acceptable. Nevertheless, insertion can be technically challenging and stent-related complications may cause recurrence [655].

Endoscopic ultrasound guided pancreatic pseudocyst drainage (EUS-PPD) is increasingly being used for management of pancreatic pseudocysts. We evaluated the outcome and complications of EUS-PPD with modified combined technique by inserting both endoprosthesis and naso-cystic drain. Forty patients referred between 2007 and 2010 for EUS-PPD were prospectively studied. EUS-PPD was attempted for symptomatic pancreatic pseudocysts which were resistant to conservative treatment, in contact with the gastric or duodenal wall on EUS and having no bulge seen on endoscopy. Controlled radial expansion wire guided balloon dilation of the puncture tract was performed followed by insertion of a 10 French double pigtail stent and 7-Fr naso-biliary drain. The early and late outcome and complications of EUS-PPD were analyzed. Thirty-two patients had non-infected and eight had infected pseudocysts. EUS-PPD was technically successful in all. Pseudocysts resolved completely in 39 patients, while one with infected pseudocyst underwent surgical resection for bleeding in the cyst. Naso-cystic drain was removed in 39 patients after median duration of 13 days. Thereafter, the double pigtail stent was removed in all cases after median duration of 10 weeks. Pseudocyst recurred in one patient requiring a second session of EUS-PPD. All 32 patients without cystic infection were successfully treated by EUS-PPD. Seven out of eight patients (87%) with cystic infection were successfully treated by EUS-PPD. Endoscopic ultrasound guided pancreatic pseudocyst drainage with modified combined technique is safe and is associated with high success rate [656].
Complication to treatment

Pancreatic pseudocyst develops as a complication in some cases of pancreatitis. Endoscopic drainage is one of the available therapies, but it has limitations when a visible compression over the gastric or duodenal wall is not present, or when portal hypertension exists. Endoscopic ultrasonography allows for a guided approach even in cases where external compression over the gastrointestinal tract is barely visible or non-existent, and it also helps to prevent vascular injury during puncture of the fluid collection. The most frequent early complications related to cystogastrostomy and cystoduodenostomy are bleeding and pneumoperitoneum, and late complications are stent migration or occlusion, and infection. We report the case of a patient who developed tense pneumoperitoneum immediately after endoscopic ultrasound guided drainage of a pancreatic pseudocyst, and was treated conservatively. This is a severe event, and can be managed by emergency decompression through paracentesis as first line therapy. Most cases of pneumoperitoneum can be managed without surgery,but close observation is mandatory in order to timely detect and treat conditions needing surgical intervention [657].

Self expandable metallic stent

Tubular plastic and metal stents have inherent shortcomings when used for transenteric drainage of fluid collections. To evaluate a novel lumen-apposing, self-expandable metal stent for EUS-guided drainage of pancreatic pseudocysts and the gallbladder a study involved 15 patients (median age 54 years) with symptomatic pancreatic pseudocysts who underwent 12 transgastric and 3 transduodenal pseudocyst drainage procedures. Five patients (median age 69.5 years) with acute cholecystitis underwent 4 cholecystoduodenostomies and 1 cholecystogastostomy. It was performed stent deployment under EUS guidance, passage of an endoscope through the stent lumen for pseudocystoscopy or cholecystoscopy. transenteric endoscopy-auided interventions includina biopsv. necrosectomy, and stone removal. All stents were successfully deployed without complication, with a median time to removal of 35 days. All pseudocysts resolved after a single drainage procedure. One stent migrated into the stomach, and the remaining 14 were found to be patent at the time of removal. There was no pseudocyst recurrence during the 11.4-month median follow-up period. One gallbladder stent remains indwelling and fully patent at 12 months. Resolution of acute cholecystitis was observed immediately after stent implantation. No recurrence of symptoms was observed during a median follow-up period of 9 months. It was concluded that transenteric drainage of pancreatic pseudocysts and the gallbladder by using a novel, lumen-apposing, metal stent was accomplished with high technical and clinical success in this pilot observational study [658].

Covered stent

Endoscopic ultrasound-guided drainage has recently been recommended for increasing the drainage rate of endoscopically managed pancreatic fluid collections and decreasing the morbidity associated with conventional endoscopic trans-mural drainage. The type of stent used for endoscopic drainage is currently a major area of interest. A covered self expandable metallic stent (CSEMS) is an alternative to conventional drainage with plastic stents because it offers the option of providing a larger-diameter access fistula for drainage, and may increase the final success rate. One problem with CSEMS is dislodgement, so a metallic stent with flared or looped ends at both extremities may be the best option. An 85-year-old woman with severe co-morbidity was treated with percutaneous approach for a large (20 cm) pancreatic pseudocyst with corpuscolated material inside. This approach failed. The patient was transferred to our institute for EUS-guided transmural drainage. EUS confirmed a large, anechoic cyst with hyperechoic material inside. Because the cyst was large and contained mixed and corpusculated fluid, we used a metallic stent for drainage. To avoid migration of the stent and potential mucosal growth above the stent, a plastic prosthesis (7 cm, 10 Fr)

with flaps at the tips was inserted inside the CSEMS. Two months later an esophagogastroduodenoscopy was done, and showed patency of the SEMS and plastic stents, which were then removed with a polypectomy snare. The patient experienced no further problems [659].

Semi-covered stent

The current therapeutic modalities for drainage of pancreatic pseudocysts include surgical, percutaneous, and endoscopic drainage modalities. Endosonography-assisted endoscopic drainage of these pseudocysts with the placement of multiple plastic or fully covered self-expanding biliary metal stents is becoming more commonly carried out. One case report discussed the unique and successful drainage of a pancreatic pseudocyst with the placement of a partially covered self-expanding metal stent [660].

In HIV/AIDS

One article described the first case of a giant pancreatic pseudocyst in a 48-year-old man with HIV infection under combination antiretroviral therapy. The patient presented with an abdominal mass involving the epigastrium, left hypochondrium, and left flank. An enhanced abdominal computed tomography (CT) scan showed a well-defined cyst of 21 cm in diameter, with a liquid content that dislocated adjacent viscera. Microbiological and cytological tests on fluid were negative, confirming diagnosis of pancreatic pseudocyst. The CT-guided percutaneous drainage was carried out and the patient's clinical condition gradually improved [661].

A risk factor for pancreatic cancer

It was examined whether the presence of pancreatic cysts could be a risk for pancreatic cancer by comparing the incidence and characteristics of cysts found by magnetic resonance (MR) imaging in patients with and without pancreatic cancer. Half-Fourier rapid acquisition with relaxation enhancement images and MR cholangiopancreatography were performed in 116 patients with pancreatic cancer (PC group) and 1226 with nonpancreatic disease (NP group). Incidence and characteristics of cysts were analyzed. Pancreatic cysts were detected in 65 patients (56 %) of the PC group and in 123 patients (10 %) of the NP group. According to the multivariate analysis, cyst presence was a significant risk factor for pancreatic cancer (odds ratio, OR, 10.3), especially cysts larger than 10 mm (OR 4.7). When the definition of cyst presence in the PC group was restricted to the 33 cases with cysts considered to have existed before the development of cancer, the incidence was still high (OR 3.0) and size remained significant (OR 4.4). Patients with pancreatic cysts, especially larger than 10 mm, were considered to be at an increased risk of pancreatic cancer over the entire pancreas [662].

Bleeding

A case of massive bleeding from gastroduodenal artery to pancreatic cyst is reported. In the literature there are only a few similar cases reported in the context of their occurrence and treatment. Bleeding was treated with gastroduodenal artery selective endovascular embolization. The article presents the classification, epidemiology and etiopathogenesis of visceral aneurysms. Consequences of aneurysm rupture were also underlined. The article lists different methods that can be used in the treatment of pseudoaneurysm with a specific estimation of endosvascular embolization in bleeding from ruptured aneurysm. The authors stress/ emphasize that arterial endovascular embolization is a mini-invasive and very effective treatment of acute bleeding from ruptured aneurysm in patients suffering from

chronic pancreatitis. It allows curing of life-threatening bleedings and avoiding emergency laparotomies during which it is often difficult to find the source of bleeding. In addition, embolization may be considered as a preoperative initial procedure that improves general patient status. It allows you to temporarily cover dangerous bleeding and later, to treat electively considering pancreatic pseudocyst [663].

A giant pseudocyst

A 56 years old man presented with epigastric pain and abdominal distension. He suffered an attack of acute pancreatitis 6 weeks back followed by pseudopancreatic cyst formation. As the cyst kept on enlarging in size despite being on conservative management, the patient was operated after 5 weeks. A huge pancreatic pseudocyst was found containing about 4.5 liters of fluid. Cystogastrostomy was performed and the patient recovered un-eventfully. It was the third largest pancreatic pseudocyst reported so far [664].

Mediastinal pseudocyst

A 62-year-old man was admitted with dyspnea. Computed tomography (CT) revealed left massive pleural effusion and a cystic lesion in the posterior mediastinal compartment extending to the pancreatic head via the esophageal hiatus. The pleural effusion had a high amylase content. Based on these findings, we diagnosed mediastinal pancreatic pseudocyst accompanied by pancreatic pleural effusion. He was treated with CT-guided puncture and endoscopic pancreatic drainage. Endoscopic pancreatic treatment is possible for pancreatic pseudocysts [665].

Concomitant pseudocyst and pseudoanaerysm

A 2 year old girl presented with recurrent abdominal pain and hematemesis. The patient was diagnosed to have chronic calcific pancreatitis complicated by pseudocyst of the head of pancreas and pseudo-aneurysm of the common hepatic artery. Diagnosis was made using abdominal ultrasonography and CT angiography. The rarity of the presentation of pseudocyst with pseudo-aneurysm formation in a pediatric patient is noted. The pseudo-aneurysm was treated by embolization of the artery and the pain being refractory to analgesics was managed by celiac plexus blockade [666].

Trombin injections in a posttraumatic aneurysm

Non-operative management for blunt injuries to the proximal pancreas has become increasingly common. A bleeding pseudoaneurysm in the setting of a traumatic pancreatic pseudocyst presents a morbid operation. It was presented a case of a 15-year old with a grade V pancreatic injury that developed a bleeding pseudoaneurysm successfully treated with percutaneous ultrasound-guided thrombin injection [667].

Experimental

One study was designed to evaluate the safety of selective transcatheter arterial embolization (TAE) with N-butyl cyanoacrylate (NBCA) in a swine model in terms of histological changes in the pancreas. Three groups of two female swine (58-64 kg) per group

underwent TAE of the dorsal pancreatic artery, under anesthesia, with 1:1, 1:4, and 1:9 mixtures of NBCA and iodized oil. Blood parameters were evaluated at days 1, 4, and 10 after TAE, after which the animals were sacrificed and pancreatic tissues were examined under light microscopy. All of the animals were asymptomatic and survived for 10 days. Cone beam computed tomographic angiography revealed occlusion of the dorsal pancreatic artery and no enhancement in the embolized area. The white blood cell count and C-reactive protein level were elevated slightly on day 1 after TAE, but they normalized or remained near the upper normal limit thereafter. The serum amylase and lipase levels also were elevated on day 1 but normalized thereafter. Histologically, necrosis and fibrosis were noted only in the embolized segment, and necrosis and acute inflammatory reactions were absent in the nonembolized segment. The border between both segments was well defined. Lymphocytic infiltration and foreign body reaction were noted around the embolized vessels. It was concluded that selective TAE with NBCA in the pancreas caused localized ischemic necrosis without clinically significant pancreatitis; therefore, this procedure is tolerable in swine [668].

Pancreatic pseudoaneurysm

Pancreatic pseudoaneurysm is a rare vascular complication of chronic pancreatitis resulting from erosion of the pancreatic or peripancreatic artery into a pseudocyst that is identified as a pulsating vascular malformation which may lead to lethal complications if left untreated. Many publications in the literature consider angiography as the first step in the management of pancreatic pseudoaneurysm to stabilize the patient's critical condition; it should be followed by surgical intervention as the definite treatment. It was reported a rare case of pancreatic pseudoaneurysm rupture with hemodynamic embarrassment in a critical patient with multiple comorbid conditions and poor risk for surgery who responded dramatically to angiographic management as a single therapeutic modality without further surgical intervention. The results observed in the patient suggest that pancreatic pseudoaneurysm may be successfully managed with angiography only and that not all cases require surgical intervention. This is particularly relevant in critically ill patients in whom surgical intervention would be unfeasible [669].

Transarterial embolization

To determine the feasibility, safety, and efficacy of adopting a standardized protocol for emergency transarterial embolization (TAE) of the gastroduodenal artery (GDA) with a uniform sandwich technique in endotherapy-failed bleeding duodenal ulcers (DU). Between 2009 and 2010, 15 patients with endotherapy-failed bleeding DU were underwent embolization. Irrespective of active extravasation, the segment of the GDA supplying the bleeding DU as indicated by endoscopically placed clips was embolized by a uniform sandwich technique with gelfoam between metallic coils. The clinical profile of the patients, re-bleeding, mortality rates, and response time of the intervention radiology team were recorded. The angioembolizations were reviewed for their technical success, clinical success, and complications. Mean duration of follow-up was 267 days. Active contrastmedium extravasation was seen in three patients (20 %). Early re-bleeding was noted in two patients (13 %). No patient required surgery. There was 100% technical success, while primary and secondary clinical success rates for TAE were 87 and 93 percent, respectively. Focal pancreatitis was the single major procedure-related complication. There was no direct bleeding-DU-related death. The response time of the IR service averaged 150 min (range 60-360 min) with mean value of 170 min. It was concluded that emergency embolization of the GDA using the sandwich technique is a safe and highly effective therapeutic option for bleeding DUs refractory to endotherapy. A prompt response from the IR service can be ensured with an institutional protocol in place for such common medical emergencies [670].

PANCREATIC TRAUMA

Blunt pancreatic trauma is rare; however, if missed, it can lead to devastating consequences such as fistula, pancreatitis, and pseudocyst. Blunt trauma accounts for 30 percent of all pancreatic injuries. High-speed motor vehicle collisions make up the greatest proportion of blunt pancreatic trauma, whereas other causes could be easily overlooked because of being so rare. In one case report it was presented a case of full-thickness transection of pancreatic tail after being kicked by a horse. The injury was timely identified and successfully treated by completing transection with a stapler. Considering that delay in diagnosis leads to a morbidity rate of 20 percent, physicians must have high level of suspicion and knowledge of invasive and noninvasive modalities to ensure early detection of pancreatic trauma and a positive outcome [671].

The management of pancreatic injuries after blunt abdominal trauma clinical data of 42 patients with blunt pancreatic injury admitted from 2001 to 2010 was analyzed retrospectively. There were 38 male and 4 female patients, aging from 13 to 65 years with a mean of 31 years. The organ injury scaling of Committee of the American Association for the Surgery of Trauma (AAST grade): grade I in 3 patients, grade II in 12 patients, grade III in 9 patients, grade IV in 13 patients and grade V in 5 patients. The mean injury severity score was 27 ± 21. Patients above AAST grade II underwent peritoneal drainage and "three neostomy" (gastrostomy, jejunostomy and gallbladder) according to damage control theory. Thirty-eight patients got abdominal CT scanning with a positive rate of 80 percent (30/38). Forty patients underwent surgical procedures, and 2 patients with non-operative management. The surgical procedures include peritoneal drainage and "three neostomy" in 32 patients, pancreas suture or pancreatic tail resection in 6 patients, pancreatoduodenectomy or caudal pancreaticojejunostomy in 2 patients. Forty patients (95 %) survived, 2 patients (5 %) died and 16 patients (38 %) had complications such as pancreatic fistula, and pulmonary infection. Abdominal CT scanning will benefit the preoperative diagnosis of blunt pancreatic trauma. Although the survival rate of patients with blunt pancreatic trauma might be improved by using the damage control surgery, the management of damage control surgery also needs to be modified because of the high rate of complications [672].

Incidence of pancreatic trauma

The objective of one study is to determine the rate of intra-abdominal injury (IAI) in adults with blunt abdominal trauma after a normal abdominal computed tomographic (CT) scan. It was hypothesize that the risk of subsequent IAI is so low that hospital admission and observation for possible IAI are unnecessary. It was conducted a prospective, observational cohort study of adults (>18 years) with blunt trauma who underwent abdominal CT scanning in the emergency department. Computed tomographic scans were obtained with intravenous contrast but no oral contrast. Abnormalities on abdominal CT included all visualized IAIs or any finding suggestive of possible IAI. Patients were followed up to determine the presence or absence of IAI and the need for therapeutic intervention if IAI was identified. Of the 3103 patients undergoing abdominal CT, 2734 (88 %) had normal CT scans. The median age was 39 years (interquartile range, 26-51 years); and 2141 (78 %) were admitted to the hospital. Eight (0.3 %; 95 % confidence interval, 0.1 to 0.6 %) were identified with IAIs after normal abdominal CT scans including the following injuries: pancreas (5), liver (4), gastrointestinal (2), and spleen (2). Five underwent therapy at laparotomy. Abdominal CT had a likelihood ratio (+) of 20.9 (95 % confidence interval, 17.7 to 24.8) and likelihood ratio (-) of 0.034 (95 % confidence interval 0.017 to 0.068). Adult patients with blunt torso trauma and normal abdominal CT scans are at low risk for subsequently identified IAI. Thus, hospitalization for

evaluation of possible IAI after a normal abdominal CT scan is unnecessary in most cases [673].

Management algoritm

The optimal management of pancreatic injuries, specifically with respect to defining ductal integrity, remains controversial. Our previous experience suggested that decisions based on probability of ductal injury might improve outcome. Consequently, a management algorithm (ALG) was developed and implemented. The purpose of this study was to evaluate the impact of this ALG on outcomes. Consecutive patients more than 13 years with pancreatic injuries subsequent to the development of the ALG were evaluated. Pancreatic injuries were defined as proximal or distal and ductal injuries classified as definite, high, low, or indeterminate (IND) probability. Pancreas-related morbidity (fistula, abscess, and pseudocyst) and mortality were recorded. Patients managed by the ALG were compared with the previous study (PS). In all, 245 patients were identified; 35 died within 12 hours and were excluded. Demographics and severity of shock (24-hour transfusions) were similar between groups. Pancreas-related morbidity for proximal injuries was 14 percent in the ALG group and 14 percent in the PS. Pancreas-related morbidity was significantly reduced in the ALG group for distal injuries requiring drainage alone (11 % vs 25 %) and for distal injuries requiring resection + drainage (26 % vs 58 %) when compared with the PS. There was no pancreas-related mortality in the ALG group (1.6 % in the PS group). It was concluded that adherence to a defined ALG simplified the management of traumatic pancreatic injuries and contributed to a reduction in both pancreas-related morbidity and mortality. The majority of all proximal pancreatic injuries can be treated with drainage alone. For distal injuries, a clinical decision based on defined parameters and suspicion of ductal injury dictates definitive management [674].

Amylas and lipase for diagnosis

Till date the function of laboratory tests in the initial assessment and subsequent management of these patients with blunt trauma is controversial. An increase in serum amylase and lipase can be caused by a broad range of conditions in the trauma patient population, which has been associated with pancreatic, hollow viscous, facial, and severe brain injuries. Apart from the pancreas, many different organs contain enzymes with lipolytic activity. Most of these organs such as tongue, esophagus, gastroesophageal junction, various sites of the stomach, duodenum, small bowel, and liver belong to the gastrointestinal tract. Many studies have supported the usefulness of laboratory evaluation in the management of blunt abdominal trauma. The serum amylase level has been of interest as a parameter for diagnosis of traumatic injury to the pancreas. There are studies to prove the role of amylase and lipase estimation as a screening diagnostic tool to detect diseases apart from acute pancreatitis. However, there is sparse literature on the role of serum and urine amylase, lipase levels, etc to help predict the specific intra-abdominal injury after blunt trauma abdomen. To elucidate the significance of elevation in the levels of amylase and lipase in serum and urine samples as reliable parameters for accurate diagnosis and management of blunt trauma to the abdomen. A prospective analysis was done on the trauma patients admitted with blunt abdomen trauma injuries over a period of six months. Blood and urine samples were collected on days 1, 3, and 5 of admission for the estimation of amylase and lipase, liver function tests, serum bicarbonates, urine routine microscopy for red blood cells, and complete hemogram. Clinical details such as time elapsed from injury to admission, type of injury, trauma score, and hypotension were noted. Patients were divided into groups according to the single or multiple organs injured and according to their hospital outcome (dead/discharged). A total of 55 patients with median age 26 (range, 6-80) years,

were enrolled in the study. Of these, 80 percent were males. Surgery was required for 20 percent of the patients. Out of 55 patients, 42 had isolated single organ injury (liver or spleen or gastrointestinal tract or kidney). Patients with pancreatic injury were excluded. In patients who suffered liver injuries, urine lipase levels on day 1, urine lipase/amylase ratio along with aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) on days 1, 3, and 5, were found to be significant. Day 1 serum amylase, AST, ALT, hemoglobin, and hematocrit levels were found significant in patients who had spleen injury. Serum amylase levels on day 5 and ALP on day 3 were significant in patients who had GIT injury. Urine amylase levels on day 5 were found to be statistically significant in patients who had kidney injury. In patients with isolated organ injury to the liver or spleen, the levels of urine amylase were elevated on day 1 and gradually decreased on days 3 and 5, whereas in patients with injury to gastrointestinal tract, the urine amylase levels were observed to gradually increase on days 3 and 5. Although amylase and lipase levels in the serum and urine are not cost-effective clinical tools for routine diagnosis of extra-pancreatic abdominal injuries in blunt abdominal trauma, but when coupled with other laboratory tests such as liver enzymes, they may be significant in predicting specific intra-abdominal injury [675].

Intramuscular autologous islet transplantation for traumatic transection

Pancreatic injuries caused by blunt trauma are often treated conservatively, except for the highest grades of these. It was reported a case of complete transection of the distal pancreas in a young adult which was successfully managed by spleen-preserving laparoscopic distal pancreatectomy followed by an islet autotransplantation in the patient's forearm striated muscle. It was thus described a mini-invasive approach for pancreatectomy with restoration of resected islets to the patient [676].

Penetrating injuries

Pancreatic injuries are uncommon but result in substantial morbidity and mortality. One study evaluated the factors associated with morbidity and mortality in civilian patients with pancreatic gunshot wounds. It was a single-institution, retrospective review of patients with gunshot wounds of the pancreas treated from 1976 to 2009 in Cape Town, South Africa. Univariable and multivariable analyses were performed. A total of 219 patients (205 male, median age 27 years) had pancreatic American Association for the Surgery of Trauma grade I-II (111 patients) and grade III-V (108) gunshot injuries to the pancreatic head (72), neck (8), body (75) and tail (64). The patients underwent 239 laparotomies, including drainage of the pancreas (169), distal pancreatectomy (59) and pancreaticoduodenectomy (11). Some 218 patients had 642 associated intra-abdominal and 91 vascular injuries. Forty-three (19.6 per cent) required an initial damage control procedure. A total of 150 patients (69 percent) had 407 postoperative complications (median 4, range 1-7). The 46 patients (21.0 per cent) who died had a median of 3 (range 1-7) complications. Median (range) intensive care unit and total hospital stay were 5 (1-153) and 11 (1-255) days respectively. Multivariable analyses identified age, high-grade pancreatic injury, associated vascular injuries and need for repeat laparotomy as predictors of morbidity. Age, shock on admission, need for damage control surgery, high-grade pancreatic injuries and associated vascular injuries were significant factors associated with mortality. It was concluded that morbidity and mortality rates were high after gunshot injuries to the pancreas. Initial shock and severe injury combined with need for damage control surgery were associated with the highest risk of death [677].

Blunt trauma

Blunt pancreatic injury is a rare type of abdominal trauma. It is a challenge to physicians due to difficulties in early diagnosis and associated complications. Most simple cases of pancreas contusion and hematoma can be safely treated conservatively. Nevertheless, the possibility of delayed mass effect and complications always exists. A 70-year-old woman with simple pancreatic head hematoma was treated conservatively. A delayed obstructive jaundice occurred 4 weeks subsequent to the trauma. Endoscopic retrograde cholangiopancreato-graphy (ERCP) with biliary stent placement provided a successful treatment instead of surgical intervention. It was concluded that a pancreatic hematoma after blunt abdominal trauma can be complicated by common bile duct obstruction with a delayed onset of obstructive jaundice. The application of ERCP with placement of a biliary stent was effective in this case. Conscientious follow-up and serial imaging studies should be utilized in patients with an initial presentation of an uncomplicated pancreatic head hematoma [678].

Endoscopic treatment

There is limited experience with pancreatic endotherapy in patients with pancreatic injury due to trauma. To retrospectively evaluate our experience of endoscopic management of pancreatic trauma 11 patients (10 males and 1 female; mean age: 22 ± 12 years) with pancreatic trauma were investigated. Patients with pseudocyst and a gastroduodenal bulge were treated with endoscopic transmural drainage. Pseudocysts without bulge or patients with external pancreatic fistula were treated with transpapillary drainage. Seven patients (6 males, 1 female) were treated for symptomatic pseudocyst and 4 patients (all males) were treated for persistent external pancreatic fistula. Three patients with external pancreatic fistula had partial disruption of pancreatic duct (head: 2 cases; tail: 1 case) and were successfully treated with bridging pancreatic stent (2 cases) or bridging nasopancreatic drain (1 case) with resolution of external pancreatic fistula in 4 to 6 weeks. Of seven patients presenting with symptomatic pseudocyst (size range: 4-14 cm), two patients were successfully treated with cystogastrostomy and there has been no recurrence over a follow up of 20 and 16 months, respectively. Five patients underwent transpapillary drainage. Three patients had partial disruption and two had complete disruption. In the former, a bridging nasopancreatic drain was placed in one patient and stent in two patients. All three patients had resolution of pseudocyst within 8 weeks and there has been no recurrence over a followup of 11 to 70 months. In two patients with complete disruption, non-bridging stent did not resolve the pseudocysts and required surgery. It was concluded that pancreatic injury due to trauma can be effectively treated endoscopically [679].

Surgery

Traumatic pancreaticoduodenal injury still remains challenging with high morbidity and mortality. Optimal management by performing simple and fast damage control surgery ensures better outcomes. A 36-year-old man was admitted with a combined pancreaticoduodenal injury after being assaulted. More than 80 percent of duodenal circumference (first portion) was disrupted and the neck of the pancreas was transected. Primary repair of the duodenum and pancreaticogastrostomy were performed. The stump of the proximal pancreatic duct was also sutured. The patient developed an intra-abdominal abscess with pancreatic fistula that eventually recovered by conservative treatment. It was concluded that pancreaticogastrostomy can be a treatment option for pancreatic transection. Rapid and simple damage control surgery with functional preservation of the organ will be beneficial for trauma patients [680].

Effect of splenectomy on blood glucose

Increasing evidence suggests that the spleen harbors stem cells that act as precursors to insulin-producing pancreas cells. Additionally, small studies with short-term follow-up associate splenectomy with increased rates of diabetes mellitus. The purpose of one study was to analyze the long-term effect of trauma splenectomy on blood glucose. Patients were included if a blood glucose level was measured more than 5 y after trauma splenectomy or laparotomy with bowel repair. Mean blood glucose level was then compared between the two groups. During the 10-year study period 61 patients underwent trauma splenectomy and 50 survived until discharge. In comparison, 229 patients underwent trauma laparotomy and bowel repair and 207 survived until discharge. Nine splenectomy patients compared with 12 control patients had, blood glucose measured at least 5 year after initial trauma. Mean followup period was not significantly different between groups (splenectomy 83 ± 18 months vs control 96 ± 44 months). In the splenectomy cohort mean glucose level was significantly higher compared with the control (114 ± 34 mg/dL vs 90 ± 13 mg/dL), as was the number of patients with recorded blood glucose level greater than 130 mg/dL (4 patient versus 0 patients). One new diagnosis of diabetes mellitus was noted only in the trauma splenectomy cohort. This small study suggests that trauma splenectomy may be associated with hyperglycemia at long-term follow-up [681].

Biliary tract trauma

Penetrating or blunt injury to the biliary tree remains a rare complication of trauma occurring in 0.1 percent of trauma admissions. Because of the different presentations, sites of biliary tract injury, and associated organ injury, there are many possible management pathways to be considered. A retrospective analysis of prospectively gathered data was performed for all gallbladder and biliary tract injuries presenting to the trauma service or hepatobiliary unit between 1999 and 2011. There were 33 biliary injuries in 30 patients (0.1 %) among 26,014 trauma admissions. Three of the 30 patients (10 %) died. Of 10 gallbladder injuries, 8 were managed with cholecystectomy. There were 23 injuries to the biliary tree. Fourteen patients had injuries to the intrahepatic biliary tree of which seven involved segmental ducts. Of these, four segmental duct injuries required hepatic resection or debridement. Nine patients had injury to the extrahepatic biliary tree of which five required T-tube placement ± bilioenteric anastomosis and one a pancreaticoduodenectomy. Thus, cholecystectomy remains the gold standard for gallbladder injury. Drainage with or without endoscopic stenting will resolve the majority of intrahepatic and partial biliary injuries. Hepaticojejunostomy remains the gold standard for complete extrahepatic biliary disruption. Hepatic and pancreatic resection are only required in the circumstances of unreconstructable biliary injury [682].

TRANSPLANTATION

Islet transplantation

Purification of islets

Islet transplantation for diabetes therapy has remained a challenge. None of the currently used transplantation sites have provided satisfactory results as islets seem to require a specific tissue for survival and growth. Since the submandibular gland (SMG) shares physiological and anatomical similarities with the pancreas, it was attempted to use this tissue as the transplantation site. In Experiment 1, a group of 10 female Syrian Golden hamsters' (SGH) received isolated and purified homologous islets transplanted into their right SMG. In Experiment 2, 15 female SGH received islet transplant into their left SMG as above, except that the recipient hamsters were made diabetic by streptozotocin (STZ) before islet transplantation. In Experiment 3, isolated and purified human islets were transplanted into the SMG of 10 female hamsters. In 8 out of 10 hamsters in Experiment 1 the islets survived and showed the same morphological structure and endocrine cell content, as intrapancreatic islets and presented signs of rapid growth and distribution. Also, as in Experiment 1, wellestablished islets were present in Experiment 2. Ten of the 15 hamsters pretreated with STZ had blood glucose values between 96 and 125 mg/dl, whereas three hamsters remained hyperglycemic (glucose levels between 194 and 417 mg/dl). Remarkably, the islets in the pancreas of 10 STZ-treated hamsters with functioning SMG islets remained atrophic even after 12 weeks. In two hamsters transplanted islets showed degeneration and remained diabetic until their pancreatic islets regenerated. In Experiment 3, transplanted human islets were completely destroyed. It was concluded that SMG appears to be the most suitable site for islet transplantation for the treatment of diabetes [683].

Effects of digestion enzymes on islet viability

The choice of enzyme blend is critical for successful islet isolation. Islet yield, viability, integrity, and function are important factors that influence the outcome of islet transplantation. Liberase HI has been used as a standard enzyme for pancreas digestion and has successfully produced islets that reversed diabetes. However, the replacement of Liberase HI with collagenase NB1 has significantly influenced the process outcome, both in quality and quantity of the isolated islets. The assessment of islet cells by flow cytometry (FC) has been reported to be useful for evaluating islet quality. The aim of this study was to assess the isolation outcomes and islet quality when comparing human islet cell processed with Liberase HI and NB1. A total of 66 islet isolations, forty-six processed using Liberase HI and twenty using Serva NB1, were retrospectively analyzed. Islet yield, function in vitro, islet cell viability by FC, as well as isolation related factors were compared. There was no significant difference in donor characteristics such as age and height, however; body mass index (BMI) in the Liberase HI group was significantly higher. There was also no significant difference in pre purification, post isolation, or post culture IEQ or percent recovery between the two groups. Flow cytometry assessment may be useful for determining the choice of digestion enzyme to maximize viable islets [684].

Laparoscopic robot-assisted pancreas transplantation

Surgical complications are a major disincentive to pancreas transplantation, despite the undisputed benefits of restored insulin independence. The da Vinci surgical system, a computer-assisted electromechanical device, provides the unique opportunity to test whether laparoscopy can reduce the morbidity of pancreas transplantation. Pancreas transplantation was performed by robot-assisted laparoscopy in three patients. The first patient received a

pancreas after kidney transplant, the second a simultaneous pancreas kidnev transplantation, and the third a pancreas transplant alone. Operations were carried out through an 11-mm optic port, two 8-mm operative ports, and a 7-cm midline incision. The latter was used to introduce the grafts, enable vascular cross-clamping, and create exocrine drainage into the jejunum. The two solitary pancreas transplants required an operating time of 3 and 5 hr, respectively; the simultaneous pancreas kidney transplantation took 8 hr. Mean warm ischemia time of the pancreas graft was 34 min. All pancreatic transplants functioned immediately, and all recipients became insulin independent. The kidney graft, revascularized after 35 min of warm ischemia, also functioned immediately. No patient had complications during or after surgery. At the longer follow-up of 10, 8, and 6 months, respectively, all recipients are alive with normal graft function. It was thus shown the feasibility of laparoscopic robot-assisted solitary pancreas and simultaneous pancreas and kidney transplantation. If the safety and feasibility of this procedure can be confirmed by larger series, laparoscopic robot-assisted pancreas transplantation could become a new option for diabetic patients needing beta-cell replacement [685]

Long-term survival

Pancreas transplantation provides the only proven method to restore long-term normoglycemia in patients with insulin-dependent diabetes mellitus. Although many studies describe the very important risk factors for short-term survival of a pancreas transplant, there is not a lot of information available about factors that distinguish short-term from long-term graft function. The analysis of 18,159 pancreas transplants from the International Pancreas Transplant Registry, performed from 25 July 1978 to 31 December 2005, showed an improvement not only in short-term but also in long-term graft function. Most recent 5-year, 10-year and 20-year graft function for transplants with the appropriate follow-up time showed 80, 68 and 45 percent, respectively, for simultaneous pancreas/kidney transplants; 62, 46 and 16 percent, respectively, for pancreas after kidney; and 59, 39 and 12 percent, respectively, for pancreas transplants factors influencing long-term function were factors that described the quality of the deceased donor. Pancreas transplants in younger or African-American recipients showed a higher risk of graft failure. Anti-T-cell induction therapy had a significant impact on long-term survival in solitary transplants [686].

Tacrolimus-induced pancreas injury

The aim of one study was to explore effects of erythropoietin and pentoxifylline in tacrolimusinduced pancreatic beta cell and renal injury in rats. Rats in group I were given saline; rats in group II were injected with tacrolimus; rats in group III were received erythropoietin (Epo) and tacrolimus; while rats in group IV were injected pentoxifylline (Ptx) plus tacrolimus for nine d. On 10th day, blood and tissue samples were taken for biochemical and pathological evaluations. Tacrolimus-injected animals exhibited significant elevation in blood urea nitrogen (BUN), and serum BUN levels were improved in rats pretreated with Ptx. Significantly more apoptotic nuclei were observed in kidneys of tacrolimus group. In rats subjected to tacrolimus and pretreated with Epo, there was significant decrease in apoptotic nuclei staining than those in tacrolimus group. Blood trough levels of tacrolimus were significantly higher in erythropoietin-pretreated group, although same amount of tacrolimus was injected with other groups. Results of the study demonstrated significant antiapoptotic effects of erythropoietin on renal tubules, increasing effect of erythropoietin on tacrolimus blood levels, and insignificant antioxidant effects of both erythropoietin and pentoxifylline on renal and pancreas tissues. Study with clinically greater tacrolimus levels may be useful to confirm these findings [687].

PANCREATIC NUTRITION

Probiotics

Probiotics are living microorganisms which, when ingested in adequate amounts, provide health benefits to the host. The mechanisms of these benefits include improved gastrointestinal barrier function, modification of the gut flora by inducing host cell antimicrobial peptides, releasing probiotic antimicrobial factors, competing for epithelial adherence, and immunomodulation to the advantage of the host. In the intensive care unit, probiotics appear to provide benefits in antibiotic-associated diarrhea, ventilator-associated pneumonia, and necrotizing enterocolitis. With increasing rates of antibiotic resistance among common nosocomial pathogens and fewer new antibiotics in the research pipeline, increasing attention has been placed on nonantibiotic approaches to the prevention and treatment of nosocomial infections. Existing studies of probiotics in critically ill patients are limited by heterogeneity in probiotic strains, dosages, duration of administration, and small sample sizes. Although probiotics are generally well tolerated and adverse events are very rare, the results of the PROPATRIA (Probiotics Prophylaxis in Patients with Predicted Severe Acute Pancreatitis) trial highlight the need for meticulous attention to safety monitoring. Better identification of the ideal characteristics of effective probiotics coupled with improved understanding of mechanisms of action will help to delineate the true beneficial effects of probiotics in various disorders [688].

Omega-3 long-chain polyunsaturated fatty acids

Inflammation is part of the normal host response to infection and injury. Eicosanoids, cytokines, chemokines, adhesion molecules and other inflammatory molecules are frequently produced during this process. Numerous studies in humans have documented the inflammation-limiting properties of omega-3 fatty acids, but only a few have been randomised clinical trials. The aim of one study was to perform a systematic search of randomised clinical trials on omega-3 fatty acids and inflammatory biomarkers in all subjects including healthy and ill persons up to February 2011 using PubMed and LILACS databases, defined by a specific equation using MeSH terms and limited to randomised clinical trials; there was no any a priori decision to include some diseases and not others. The quality of each publication was validated by using the JADAD scale and the CONSORT checklist. Inflammatory biomarkers were considered as primary outcomes. Twenty-six publications of the last 10 years were selected. Studies included healthy subjects and patients with cardiovascular disease and other chronic and acute diseases; all reported the number of subjects, type of study, type and doses of omega-3 fatty acids, main outcomes and major inflammatory biomarkers. Dietary omega-3 fatty acids are associated with plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation in cardiovascular disease and other chronic and acute diseases, including chronic renal disease, sepsis and acute pancreatitis. However, further research is required before definitive recommendations can be made about the routine use of omega-3 fatty acids in critically ill patients or with neurodegenerative or chronic renal disease [689].

Enteral feeding patients with gastric outlet obstruction

Patients with upper gastrointestinal obstructions were previously managed with gastric decompression and parenteral feeding. The authors present their experience in 50 patients with obstructions chiefly due to complicated severe acute (n=31) or chronic cystic pancreatitis (n=11) using a double-lumen nasogastric decompression and jejunal feeding tube system held in place with a nasal bridle that passes through the obstructed

gastroduodenal segments, allowing distal jejunal feeding, and at the same time decompresses the stomach to prevent vomiting and aspiration. The tip of the jejunal tube was placed approximately 40 cm down the jejunum to maintain pancreatic rest. Duration of feeding ranged from 1-145 days (median 25 days); 19 patients were discharged home with tube feeds. Only 1 patient could not tolerate feeding and needed to be converted to parenteral feeding. Average tube life was 14 days, with replacement being needed most commonly for kinking or clogging of the jejunal tube (56 %) or accidental dislodgement (24 %). The obstruction resolved spontaneously in 60 percent, allowing resumption of normal eating. Of the patients with severe acute pancreatitis or pancreatic pseudocysts, pancreatic rest resulted in resolution of the disease without surgery in 87 percent, and need for surgery in the remainder was put off for 31-76 days. Seven patients died predominantly of complications of acute pancreatitis between 1 and 31 days. In conclusion, nasogastro- or jejuna feeding feeding provides a relatively safe conservative management for critically ill patients with upper gastrointestinal obstructions, reducing the need for surgery and parenteral feeding [690].

Vegan diet

In a previous study, it was demonstrated that abstaining from meat, for 1 month, by healthy omnivores (lacto-ovovegetarian model) resulted in a statistical decrease in pancreatic secretion as measured by faecal elastase-1 output. However, no correlation between relative and non-relative changes of energy and nutrient consumption and pancreatic secretion was documented. Therefore, in another study, it was aimed to assess the changes of exocrine pancreatic secretion with a more restrictive dietetic modification, by applying a vegan diet. A total of twenty-one healthy omnivores (sixteen females and five males) participated in the prospective study lasting for 6 weeks. The nutrient intake and faecal output of pancreatic enzymes (elastase-1, chymotrypsin and lipase) were assessed twice during the study. Each assessment period lasted for 7 d: the first before the transition to the vegan diet (omnivore diet) and the second during the last week of the study (vegan diet). The dietary modification resulted in a significant decrease in faecal elastase-1 and chymotrypsin output. The lipase excretion remained unchanged. The decrease in proteolytic enzymes was documented to be positively correlated with a decreased protein intake. In addition, elastase-1 and chymotrypsin outputs were also related to the changes of protein type, plant versus animal. It was concluded that significant reduction and modification of protein intake due to a shortterm vegan diet [691].

PANCREATIC INFECTIONS

HIV

Little data are available for HIV-positive patients regarding pancreatic cancer. The aim of this study was to investigate and to compare clinical presentation and outcome between HIV-positive and HIV-negative PC patients. From 1988 to 2010, the Italian Cooperative Group on AIDS and Tumors identified 16 cases of HIV-positive PC patients. Each HIV-positive patient from our institution was randomly matched (ratio 1:2) with HIV-negative patients (32 controls) based on sex and year of PC diagnosis. Differences in clinical presentation, treatment, and overall survival were assessed. At multivariate analysis, HIV-positive patients compared with HIV-negative patients had a higher risk of an unfavorable performance status (PS \geq 2) and a younger age (<50 years) at cancer diagnosis. At multivariate analysis, HIV-positive status and PS of 2 or greater were the only 2 features that significantly reduced PC patients' survival. The data show, for the first time, that HIV-positive PC patients, compared with HIV-negative patients, are younger at cancer diagnosis. Furthermore, they share a more unfavorable PS and a shorter survival [692].

To assess the incidence of acute pancreatitis in human immunodeficiency virus-positive patients with triglyceride (TG) greater than 500 mg/dL after highly active antiretroviral therapy sequential TG levels during follow-up and episodes of acute pancreatitis were retrospectively reviewed in 347, 417, and 571 patients enrolled in periods 1 (2000-2002), 2 (2003-2005), and 3 (2006-2008), respectively. The incidence of acute pancreatitis, defined as consistent clinical symptoms and elevated amylase and/or lipase levels, was estimated. A total of 5356 TG measurements were performed during the follow-up for 698, 884, and 1215 person-years in periods 1, 2, and 3, respectively. Overall, 10 percent of patients had at least one TG greater than 500 mg/dL. Five patients with TG less than 500 mg/dL developed acute pancreatitis. The crude incidences of acute pancreatitis were 0.6, 0.5, and 0.2, and the incidence rates were 2.86, 2.26, and 0.82/1000 person-years in periods 1, 2 and 3, respectively. The incidence rates of acute pancreatitis when TG levels were less than 500, less than 1000, and less than 1500 mg/dL ranged from 1.2 to 4.9/1000 person-years, whereas it was 0/1000 person-years when TG levels were greater than 500, greater than 1000, and greater than 1500 mg/dL, respectively. It was concluded that the risk of acute pancreatitis was low among human immunodeficiency virus-positive patients who developed hypertriglyceridemia after receiving highly active antiretroviral therapy [693].

One present paper described possible connections between antiretroviral therapies (ARTs) used to treat human immunodeficiency virus (HIV) infection and adverse drug reactions (ADRs) encountered predominantly in the liver, including hypersensitivity syndrome reactions, as well as throughout the gastrointestinal system, including the pancreas. Highly active antiretroviral therapy (HAART) has a positive influence on the quality of life and longevity in HIV patients, substantially reducing morbidity and mortality in this population. However, HAART produces a spectrum of ADRs. Alcohol consumption can interact with HAART as well as other pharmaceutical agents used for the prevention of opportunistic infections such as pneumonia and tuberculosis. Other coinfections that occur in HIV, such as hepatitis viruses B or C, cytomegalovirus, or herpes simplex virus, further complicate the etiology of HAART-induced ADRs. The aspect of liver pathology including liver structure and function has received little attention and deserves further evaluation. The materials used provide a data-supported approach. They are based on systematic review and analysis of recently published world literature (MedLine search) and the experience of the authors in the specified topic. It was conclude that therapeutic and drug monitoring of ART, using laboratory identification of phenotypic susceptibilities, drug interactions with other medications, drug interactions with herbal medicines, and alcohol intake might enable a safer use of this medication [694].

Herpes simplex

The most common causes of pancreatitis in adults are alcohol and biliary tract disease, whereas abdominal trauma, systemic disease, and idiopathic disease are the principal causes in childhood. The incidence of acute pancreatitis in children has increased significantly over the last decade. There are several causes of acute pancreatitis, and infectious agents constitute only a small percentage. Viral agents such as mumps virus, cytomegalovirus (CMV), coxsackievirus, herpes zoster virus, Epstein-Barr virus (EBV), rubella, and adenoviruses have been reported in a few cases in literature. Herpes simplex virus (HSV) has been implicated in only a few reported cases, and it was now presented the first case in literature of acute viral pancreatitis in an immunocompetent 13-year-old boy. Herpes simplex virus is an enveloped, double-stranded DNA virus that causes infection of mucosal surfaces and rarely leads to disseminated visceral infection in neonates or immunocompromised adults. The boy was admitted to the emergency department with acute abdominal pain associated with vomiting that started a few hours before admission. No fever was reported. The patient had recently undergone a laparoscopic appendectomy, and he had been discharged on the third postoperative day in good conditions. Physical examination showed diffused abdominal tenderness and guarding. Blood tests revealed an increase of serum amylase (1125 IU/L; reference range, <100 IU/L) and lipase (727 IU/L; reference range, 16-63 IU/L). White blood cell count, electrolyte values, liver function, and renal function were within normal limits. An abdominal ultrasound was performed at admission, and no liver, gallbladder, or pancreatic anomalies were found. The patient tested positive for IgM anti-HSV, immunization for rubella (high IgG tritate), and negative for IgM anti-CMV, anti-EBV, and Toxoplasma gondii. The patient was treated conservatively for acute pancreatitis, and oral feedings were initiated 72 hours after the admission and were well tolerated. After 3 months, the child is well, and serum sample showed seroconversion [695].

Tuberculosis

Pancreatic tuberculosis (TB) is a rare disease. It can be easily confused with malignancy or pancreatitis on imaging. This could result in unnecessary surgery. Pancreatic TB is uncommon even in endemic areas. In a large series of 300 cases from India with abdominal TB, there were none with pancreatic TB. A recent review reported that 23 percent of the 62 reported cases of pancreatic TB occurred in patients who were HIV positive. The clinical features of pancreatic TB are protean and include weight loss (69 %), anorexia, abdominal pain (75 %), fever, night sweats, back pain and jaundice (31-40 %). Patients may present with obstructive jaundice and a pancreatic mass lesion that is clinically indistinguishable from a pancreatic neoplasm. Some patients may present with a pancreatic cyst or an abscess which can be mistaken for a cystic neoplasm or an infected pseudocyst. Pancreatic TB has also been reported to cause acute pancreatitis, portal hypertension, intra-abdominal haemorrhage via direct invasion of a peripancreatic artery, chronic pancreatitis and diabetes. A case report of pancreatic TB presenting as a head mass along with a pancreatico-biliary fistula has also been reported. There are no pathognomic radiological features of pancreatic TB. CT findings include hypodense lesions with irregular borders usually in the head of the pancreas, diffuse enlargement of the pancreas or enlarged peripancreatic lymph nodes. Magnetic resonance imaging (MRI) findings of focal pancreatic TB include a sharply delineated mass usually located in the pancreatic head, showing heterogenous enhancement. These lesions are characteristically hypointense on fat-suppressed T1weighted images and show a mixture of hypo/hyper intensity on T2-weighted images. The common bile duct and the pancreatic duct have been reported to be normal in patients with pancreatic TB. even if the mass is positioned centrally in the head of the pancreas. This is in sharp contrast to adenocarcinoma of the pancreas where the pancreatic duct is dilated in centrally located tumours of the pancreatic head. The diffuse form of pancreatic TB is

characterized by pancreatic enlargement with narrowing of the main pancreatic duct and heterogeneous enhancement. Endoscopic retrograde cholangio-pancreatography is usually not helpful, although there have been case reports of biliary cytology confirming the diagnosis. Due to the lack of pathognomic radiological features for pancreatic TB, most cases have been diagnosed in the past at laparotomy performed for a suspicion of pancreatic malignancy. Few cases have been diagnosed by fine needle aspiration cytology/biopsy with a success rate ranging from 50 to 62 percent. It was reported three cases of pancreatic tuberculosis that were diagnosed by endoscopic ultrasound. In conclusion, endoscopic ultrasound is the diagnostic modality of choice for pancreatic tuberculosis facilitating high resolution imaging, as well as sampling of tissue for staining, cytology, culture and polymerase chain reaction assay [696].

Tuberculosis and HIV

Pancreatic tuberculosis (TB) is a relatively rare disease that can mimic carcinoma, lymphoma, cystic neoplasia, retroperitoneal tumors, pancreatitis or pseudocysts. It was reported a case of a 31-year-old immigrant Burmese woman who exhibited epigastralgia, fever, weight loss and an epigastric mass. The patient was diagnosed with pancreatic TB and acquired immunodeficiency syndrome, and was treated with antituberculous drugs and percutaneous catheter drainage without a laparotomy. The clinical presentation, radiographic investigation and management of pancreatic TB are summarized in this paper to emphasize the importance of considering this rare disease in the differential diagnosis of pancreatic masses concomitant with human immunodeficiency virus infection. I also emphasize the need for both histopathological and microbiological diagnosis via fine-needle aspiration [697].

Hydatide infection

Primary pancreatic hydatid cysts are rare and its percutaneous treatment and catheterization technique has, to the best of our knowledge, not been published in literature. A 33-year-old male patient who presented with abdominal pain was evaluated by ultrasonography (US) and computed tomography examinations. Both examinations revealed a cyst in the neck of the pancreas. After the administration of albendazole chemoprophylaxis, the patient underwent diagnostic puncture showing high pressure spring water which harbored the scoleces and was treated percutaneously by the catheterization technique. In this technique, first the cyst was punctured, the fluid content aspirated, the radiocontrast material injected to see possible fistulisation, and then re-aspirated. The 20 percent hypertonic saline solution was injected and re-aspiration was performed to the best of our abilities, followed by the insertion of a catheter for drainage of the remaining non-aspiratable fluid content. At follow-up examination, the cyst was not visible on US after 6 months. There was no evidence of cyst recurrence or dissemination after 18 months at serologic and imaging follow-up [698].

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