

REVIEW OF LITERATURE ON CLINICAL PANCREATOLOGY

Scientific literature made available in 2011

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REVIEWER'S PREFACE (AND SEARCH ALGORITHM)

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 collection of full articles printed and made available in Stockholm the first half year of 2011 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 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 choices (on the other hand: it is up to the reader to read or not!).

There must be made some limitations, otherwise a review in this format should not be possible to write due to lack of time and lack of brain capacity, and probably not possible to read either – it is not meant to be only for masochists. Regarding the limitations, first of all only some of the articles have been read in their full length, but the writing here is mostly 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 introductory sample that hopefully will make the reader eager to read the whole article or articles: “a taste of clinical pancreatology in the first two quarters of 2011”.

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*, *pancreatic cancer*, *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 purely 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 uninteresting, but because they are so numerous, and because it is much more difficult to evaluate the importance of them. Some new articles may seem to be of little importance today, but might be the first paper of a new paradigm – other may represent the reverse.

I have been asked if some of the items are not stolen from other journals, but I can assure you that ALL is carefully copied. I see this summaries only as a way of spreading other's cumbersome work to a broader audience. ALL is copied, and that is the meaning – of course always with the full reference.

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, welcome with comments – and if the comments fail to appear, the next quarters and year will have the same disposition as the present. Welcome back next quarter!

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 - Gemcitabine \pm radiation
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 - Cetuximab, gemcitabine, and oxaliplatin
 - Capecitabine and temozolomide
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 - Gemcitabine, bevacizumab, and radiotherapy
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 - Drug resistance
 - High-intensity focused ultrasound (HIFU)
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- Natural history of branch duct IPMNs
- Growth rate

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Prognostic factors

Tumor markers

- Mural nodules

After resection

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- CT

- MRI

- Cyst fluid K-ras

- CEA and cytology

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- FDG accumulation

- CT versus MRI

- MDCT ± MRI

NON-NEOPLASTIC CYSTIC PANCREATIC TUMORS

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Benign epithelial cyst

Necrosis

Abscess

Duodenal diverticulum

Lymphoepithelial cyst

Mucinous nonneoplastic cyst

NON-PANCREATIC PERIAMPULLARY TUMORS

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- Endoscopic resection of ampullary adenomas

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- CD99

Acinar cell carcinoma

Spindle cell tumors

Mixed ductal-endocrine carcinoma

Osteoclastic giant cell tumor

Anaplastic cancer

Mucinous adenocarcinoma

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- Chromogranin A in ascites
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- In cancer

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- Damage control laparotomy

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- Hepatitis E
- Actinomycosis
- CMV

REFERENCES

ABBREVIATIONS

AAA	abdominal aortic aneurysm
AAST	American Association for the Surgery of Trauma
ACC	acinar cell carcinoma
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
aCGH	array comparative genomic hybridization
ACGME	Accreditation Council for Graduate Medical Education
ACP	alcoholic chronic pancreatitis
ACS	abdominal compartment syndrome
ADC	apparent diffusion coefficient
ADH	alcohol dehydrogenase
ADS	anesthesiologist-directed sedation
AEBR	arterial en bloc resection
aFGF	acidic fibroblast growth factor
AFP	alpha-fetoprotein
AGT	abnormal glucose tolerance
AICR	American Institute for Cancer Research
AIP	autoimmune pancreatitis
AJCC	American Joint Committee on Cancer
ALC	acne lesion counting
ALDH	aldehyde dehydrogenase
ALI	acute lung injury
ALL	acute lymphoblastic leukemia
AMPK	AMP-activated protein kinase
AMY	amylase
Ang	angiopoietin
ANGT	angiopoetin
AP	acute pancreatitis
AP	anterior-posterior
APACHE	Acute Physiology and Chronic Health Examination
APC	advanced pancreatic cancer
AR	arterial resection
ARPD	augmented regional pancreatoduodenectomy
ASA	American Society of Anesthesiologists
ATP	adenosine-5-triphosphate
AT1R	angiotensin II type 1 receptor
AUC	area under receiver operating curve
AZA	azathioprine
BF	blood flow
bFGF	basic fibroblast growth factor
BD-IPMN	branch-duct intraductal papillary mucinous neoplasm
BMD	bone mineral density
BMI	body mass index
BPN	broad plexus neurolysis
Br-IPMN	branch duct intraductal papillary mucinous neoplasm
BT-PABA	N-benzoyl-L-tyrosyl-p-aminobenzoic acid
BUN	blood urea nitrogen
BV	blood volume
CA	carbohydrate antigen
CA 19-9	carbohydrate antigen 19-9
CABG	coronary-artery bypass grafting
CASMAD	combined aortic and superior mesenteric artery dissection
CBD	common bile duct

CB1R	cannabinoid 1 receptor
CCA	Cancer Council Australia
CCCW	Comprehensive Cancer Centre West
CCK	cholecystokinin
CCRT	chemoradiotherapy
CD	cumulative dose
CD	Crohn's disease
CDC	choledochoduodenostomy
CDK	cyclin-dependent kinase
CDS	choledochoduodenostomy
CEA	carcinoembryonic antigen
CECT	contrasted-enhanced computed tomography
CEL-MODY	carboxyl ester lipase gene-maturity onset diabetes of the young
CEUS	of contrast-enhanced ultrasound
CF	cystic fibrosis
CFA	coefficient of fat absorption
CG	cholesterol granuloma
CgA	chromogranin-A
CGN	celiac ganglia neurolysis
CHASM	Cancer-specific High-throughput Annotation of Somatic Mutations
CI	confidence interval
CLDN	claudin-18
CLP	cystic lesions of the pancreas
CMS	Centers for Medicare and Medicaid Services
CNC	Carney complex
CONKO	Charité Onkologie
COSMIC	Catalog of Somatic Mutations in Cancer
COX	cyclo-oxygenase
CP	chronic pancreatitis
CPB	celiac plexus block
CPN	celiac plexus neurolysis
CRC	colorectal carcinoma
CRS	comprehensive risk score
CRT	chemoradiation
CSC	cancer stem cells
CSEMS	silicon-covered self-expandable metal stent
CSS	cancer specific survival
CT	computed tomography
CT	chemotherapy
CTC	counting circulating tumor cells
CTC	common toxicity criteria
CTLA	cytotoxic T-lymphocyte-associated antigen
CTRC	chymotrypsin C
CTSI	CT severity indices
CUR	curcumine
CW	classic Whipple
DALY	disability adjusted life years
DBD	donors with brain death
DC	dendritic cell
DCE	dynamic contrast material-enhanced
DCL	damage control laparotomy
4D-CT	using four-dimensional computed tomography
DD	delayed diagnosis
DDW	Digestive Disease Week
DF	desmoplastic fibroblastoma

DFS	disease-free survival
DGE	delayed gastric emptying
DLP	dose-length product
DLT	dose limiting toxicity
DM	diabetes mellitus
DNMT	DNA methyltransferases
DOPPHR	duodenum and organ-preserving pancreatic head resection
DP-CAR	distal pancreatectomy with en bloc celiac axis resection
DM	diabetes mellitus
DPD	dihydropyrimidine dehydrogenase
DPP-4	dipeptidyl peptidase-4
DPPHR	duodenum-preserving pancreatic head resection
DSF	disulfiram; 1-(diethylthiocarbamoyldisulfanyl)-N,N-diethylmethanethioamide
DT	doubling time
DW	diffusion-weighted
DWI	diffusion-weighted imaging
EB	embryoid body
EBD	endoscopic biliary drainage
EBHR	evidence-based hospital referral
EBL	estimated blood loss
EBRT	external beam radiotherapy
EC	endogenous cannabinoid
ECOG	Eastern Cooperative Oncology Group
EGDS	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMSA	electrophoretic mobility shift assay
EMT	epithelial-mesenchymal transition
ENETS	European Neuroendocrine Tumors Society
ENPD	endoscopic nasopancreatic drainage
EOPC	early onset pancreatic cancer
E-path	electronic pathology reporting
EPI	exocrine pancreatic insufficiency
EPLBD	endoscopic papillary large balloon dilatation
EPO	erythropoietin
ERBD	endoscopic retrograde biliary
ERCP	endoscopic retrograde cholangiopancreatography
ERP	endoscopic retrograde pancreatography
ESA	erythropoiesis-stimulating agents
ESC	embryonic stem cells
EST	endoscopic sphincterotomy
ESWL	extracorporeal shock wave lithotripsy
EPS	endoscopic pancreatic stenting
ESPAC	European Study Group for Pancreatic Cancer
ETS	endoscopic transpapillary stenting
EUS	endoscopic ultrasound
EUS-EL	endoscopic ultrasound-guided ethanol lavage
EUS-FNA	endoscopic ultrasound guided fine-needle aspiration
EUS-TCB	endoscopic ultrasonography-guided trucut biopsy
EXPeRT	European cooperative study group for paediatric rare tumours
FA	folinic acid
FA	fractional anisotropy
FAP	familial adenomatous polyposis
FBG	fasting blood glucose
FCPL	focal cystic pancreatic lesions

FCRL	Fc receptor-like
FE	faecal elastase
FFLP	freedom from local progression
FFPE	formalin-fixed, paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptors
FLA	focal lobular atrophy
FNA	fine needle aspiration
FOLFIRINOX	oxaliplatin, irinotecan, fluorouracil, and leucovorin
FPC	familial pancreatic cancer
FPTR	Familial Pancreatic Tumor Registry
GAGS	global acne grading scale
GBC	gemcitabine-based chemotherapy
GCK	glucokinase
GDS	gastroenterologist-directed sedation
GE	gastric emptying
GEL	granulocyte epithelial lesion
GEM	gemcitabine
GEMOX	gemcitabine and oxaliplatin
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GFF	gemcitabine, 5-fluorouracil (5-FU) and folinic acid
GFPT	glutamine-fructose-6-phosphate transaminase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GITSG	Gastrointestinal Tumor Study Group
GLP	glucagon-like peptide
GLP-1	glucagonlike peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GTX	gemcitabine, docetaxel, and capecitabine
HELLP	hemolysis, elevated liver enzymes, low platelet count
hENT	human equilibrative nucleoside transporter
hESC	human embryonic stem cells
HEV	hepatitis E virus
HGA	high-grade atypia
HGD	high-grade dysplasia
hIAPP	human islet amyloid polypeptide
HIF	hypoxia-inducible factor
HIFU	high-intensity focused ultrasound
HISORt	histology, imaging, serology, other organ involvement, and response to steroids
HK2	hexokinase 2
HOP	head of pancreas
HPG	hepatic glucose production
HR	hazard ratios
HPF	high-power field
HPG	hepatic glucose production
HR	hazard ratios
HSP	Henoch-Schönlein purpura
HU	Hounsfield units
HuREPO	human recombinant erythropoietin
HT	regional hyperthermia
HVH	high-volume hospital
IAC	immunoglobulin G4 associated
IAPP	Islet amyloid polypeptide (amylin)
IAT	islet autotransplantation

ICDC	international consensus diagnostic criteria
ICG	international consensus guidelines
ICP	idiopathic chronic pancreatitis
ICU	intensive care unit
IDCP	idiopathic duct centric pancreatitis
iFAM	infusional 5-fluorouracil, doxorubicin, and mitomycin-C
IGF	insulin like growth factor
IGF-1R	insulin like growth factor-1 receptor
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgG4-RSD	IgG4-related systemic disease
IHC	immunohistochemical
IKKepsilon	IkappaB kinase
ILD	induced interstitial lung disease
ILI	intensive lifestyle intervention
IMRT	intensity-modulated radiation therapy
IOI	imaging-to-operation interval
IORT	intraoperative radiotherapy
IP	idiopathic pancreatitis
IPDA	inferior pancreaticoduodenal artery
IPMA	intraductal papillary mucinous adenoma
IPMC	intraductal papillary mucinous carcinoma
IPMN	intraductal papillary mucinous tumors
IPN	infected pancreatic necrosis
IPN	intraductal papillary neoplasm
IPNB	intraductal papillary neoplasms of the bile duct
IQR	interquartile range
IR	interventional radiology
IR	ionizing radiation
IR	insulin receptor
IRAP	idiopathic recurrent acute pancreatitis
ISD	IgG4-associated systemic disease
ISGPF	International Study Group on Pancreatic Fistula
ISL1	islet 1 gene product
ITPN	intraductal tubulopapillary neoplasm
IV	intravenously
JHH	Johns Hopkins Hospital
JSAP	Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer
KGF	keratinocyte growth factor
KLF	Krüppel-like factor
LAPS	locally advanced pancreatic cancer
LBC	liquid-based cytology
LEC	lymphoepithelial cysts
LGD	low-grade dysplasia
LHR	liver receptor homologue
LINE	long interspersed nuclear element
LIP	lipase
LIPS	lung injury prediction score
LIS	liver susceptometry
LLP	laparoscopic left pancreatectomy
LKB1-AMP	liver kinase B1-adenyl monophosphate (LKB1-AMP)
LNR	the lymph node ratio
LOH	loss of heterozygosity
LOS	length of stay
LPJ	lateral pancreaticojejunostomy

LPL	lipoprotein lipase
LPS	lipopolysaccharide
LPSP	lymphoplasmacytic sclerosing pancreatitis
LR	left-right
MA	mucinous adenocarcinoma
mAbs	monoclonal antibodies
MAD	matrix academic division
MCN	mucinous cystic neoplasm
MCTSI	modified CT severity index
MD	mean differences
MDCT	multidetector computed tomography
MD-IPMN	main pancreatic duct-IPMN
2ME2	2-methoxyestradiol
MetS	metabolic syndrome
MFP	mass-forming pancreatitis
MIPN	minimally invasive pancreatic necrosectomy
miRNA	microRNA
MMP	matrix metalloproteinases
MN	mural nodule
MNC	mucinous nonneoplastic cysts
MnSOD	manganese superoxide dismutase
MPD	main pancreatic duct
MPL	mass-per-length
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatogram
MRI	magnetic resonance imaging
MSCT	multislice computed scanner
MST	median survival time
MTD	maximum tolerated dose
MUC	mucin
MVD	microvessel densities
nACh	nicotine acetylcholine
NCCN	National Comprehensive Cancer Network
NCD	non-communicable disease
NDMA	p-nitrosodimethylaniline
NEN	neuroendocrine neoplasms
NET	neuroendocrine tumors
nfnePC	non-functioning neuroendocrine pancreatic carcinoma
NFPTR	National Familial Pancreas Tumor Registry
NGN3	neurogenin 3 gene product
NGT	normal glucose tolerance
NHL	non-Hodgkin's lymphoma
NEN	neuroendocrine neoplasms
NFPTR	National Familial Pancreas Tumor Registry
NHL	non-Hodgkin's lymphoma
NK	natural killer
NPV	negative predictive value
NSCLC	non-small-cell lung cancer
OF	organ failure
OGTT	oral glucose tolerance tests
OLP	open left pancreatectomy
OPN	osteopontin
OPRT	orotate phosphoribosyltransferase
OR	odds ratio
OS	overall survival

OT	operative time
PA	pancreatic adenocarcinoma
PAM	pancreatic serum amylase
PanIN	pancreatic intraepithelial neoplasia
PanNET	pancreatic neuroendocrine tumors
PAP	pancreatitis associated protein
PAS	periodic acid-Schiff
p-Atk	phosphorylated Akt
PBMC	peripheral blood mononuclear cells
PBP	plasminogen binding protein
PC	pancreatic cancer
PCD	percutaneous catheter drainage
PCDAI	pediatric Crohn's disease activity index
PCL	pancreatic cystic lesion
PD	pancreatoduodenectomy
PD	pancreas divisum
PD	pancreatic duct
PDA	pancreatic ductal adenocarcinoma
PDAC	pancreatic ductal adenocarcinoma
PDS	polydioxanone
PDTC	dithiocarbamate
PDX	pancreatic and homeobox protein
PDX1	pancreatico-duodenal homeobox 1
PECom	perivascular epithelioid cell neoplasm
PEDF	pigment epithelium-derived factor
PEG	percutaneous endoscopic gastrostomy
PEI	pancreatic exocrine insufficiency
PEP	postendoscopic retrograde cholangiopancreatography pancreatitis
PEP	post-ERCP pancreatitis
PET	positron-emission tomography
PET	pancreatic endocrine tumor
PF	pancreatic fistula
PFI	pancreatic fungal infection
PFS	progression-free survival
PG	pancreaticogastrostomy
PGY	postgraduate year
PI	pancreatic insufficiency
PIGF	placental growth factor
PI3K	phosphatidylinositol 3-kinase
PIMS	Pathology Information Management System
PIP	pancreatic insufficiency prevalence
PJ	pancreaticojejunostomy
PLRP	pancreatic lipase-related protein
PMA	phorbol 12-myristate 13-acetate
PNET	pancreatic neuroendocrine tumors
P-NET	pancreatic neuroendocrine tumor
PNI	prognostic nutrition index
PNSO	professional network of surgical oncologists
POPF	postoperative pancreatic fistulae
PP	pancreatic polypeptide
PPAR	peroxisome proliferator-activated receptor
PPF	postoperative pancreatic fistula
PPI	proton-pump inhibitors
PPPD	pylorus-preserving pancreatoduodenectomy
PPS	prophylactic pancreatic stents

PPV	positive predictive value
PPW	pylorus-preserving pancreaticoduodenectomy
PR	partial response
PrPD	pylorus-resecting pancreatoduodenectomy
PRRT	peptide receptor radioligand therapy
PS	performance status
PS	permeability surface
PSC	primary sclerosing cholangitis
PSTI	pancreatic secretory trypsin inhibitor
PSP	pancreatic stone protein
PTBD	percutaneous transhepatic biliary drainage
PTEN	phosphatase and tensin homolog
PSP	pancreatic stone protein
PTBD	percutaneous transhepatic biliary drainage
QOL	quality of life
QoL	quality of life
RAP	recurrent acute pancreatitis
RC	Rosemont criteria
RCC	renal cell carcinoma
RCT	randomised controlled trials
RDT	reciprocal of doubling time
RECIST	response evaluation criteria in solid tumours
RFC	recurrence free survival
ROC	receiver operating characteristic
ROS	reactive oxygen species
RR	relative risks
RT	radiotherapy
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
RUB	rubusoside
RVU	relative value unit
RYGB	Roux-en-Y gastric bypass surgery
SAE	severe adverse events
SAP	severe acute pancreatitis
SB-IPMN	side branch-IPMN
SBRT	stereotactic body radiotherapy
SCC	Spearman correlation coefficient
SCN	serous cystic neoplasms
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SF-12	Short Form-12
SG	surgical gastrostomy
Shh	sonic hedgehog
shRNA	short hairpin RNA
SI	stimulatory indices
SI	superior-inferior
SIR	standardized incidence ratio
siRNA	small interfering RNA
SISMAD	superior mesenteric artery dissection
SL	staging laparoscopy
SMA	superior mesenteric artery
SMA	smooth muscle actin
SMEAR	smear method
SMV	superior mesenteric artery vein
SNP	single nucleotide polymorphisms

SNR	signal-to-noise ratio
SPARC	secreted protein acidic and rich in cysteine
SPC	solid pseudopapillary carcinoma
SPINK	serine protease inhibitor Kazal
SPN	solid-pseudopapillary neoplasms
SPT	solid pseudopapillary tumor
SRC	signet ring cell carcinoma
SSA	somatostatin analogues
SSS	surgical stress score
SST	somatostatin
SSTR	somatostatin receptors
STM	standardized test meal
TCB	tru-cut biopsy
TCM	traditional Chinese medicine
TCP	tropical calcific pancreatitis
TGF	transforming growth factor
TF	transcription factor
TF	tissue factor
TFPI	tissue factor inhibitor
TG	triglyceride
TG-ERCP	transgastrostomy ERCP
T1HLPtType 1	hyperlipoproteinemia
TIC	time-intensity curve
TNF	tumor necrosis factor
TIMP	tissue inhibitor of metalloproteinase
TNM	tumor-node-metastasis
TP	total pancreatectomy
TPMT	thiopurine methyl transferase
Treg	regulatory T cell
TS	trauma scan
TS	thymidylate synthase
TZD	thiazolidinediones
UEGW	United European Gastroenterology Week
UFT	uracil/tegafur
UGI	upper gastrointestinal
UM	unanticipated metastasis
US	ultrasound
US	ultrasonography
USgHIFU	ultrasound-guided high-intensity focused ultrasound
USSI	ultrasound severity indices
VA	Veterans Affairs
VAS	visual analogue scale
VDCC	voltage-dependent calcium channel
VEGF	vascular endothelial growth factor
VTE	thromboembolism
WBRT	whole brain radiation therapy
WCRF	World Cancer Research Fund
WHO	World Health Organization
WM	western medicine
WMD	weighted mean differences
YLL	years of life lost

THEORY ON CLINICAL RESEARCH

Merits of clinical research

In the age of evidence-based medicine, clinical trials are playing an increasingly central role. While the approval of new medicinal products justifiably requires phase III randomized controlled trials, diagnostic procedures and nonpharmacological therapies should likewise be subjected to needs assessments and risk assessments using the criteria of evidence-based medicine. Consequently, the future of clinical research – and with it also the future of medical decision making – will be based to a large extent on prospective clinical studies. In keeping with the rising standards, most good medical journals now carry a section on “clinical trials” or even “randomized clinical trials” because such studies engender prestige and citations in the publishing world. The Federal Coordinating Council for Comparative Effectiveness Research, the UK National Institute for Health Research, and the German medical research funding organizations, such as the Deutsche Forschungsgemeinschaft (German Research Foundation) and the Bundesministerium für Bildung und Forschung (Ministry for Education and Research), all now support clinical trials as well as systematic reviews and meta-analyses. Despite all these efforts and despite clearly positive developments in the direction of more evidence-based medicine, now as before, there remains a huge gap between intention and reality: there are far too few appropriately powered clinical trials that can justifiably be used to influence, even partially, the practice of medicine and surgery. Good clinical trials – especially when they are multicenter – are cumbersome. They require complex, long-term planning, are difficult to execute due to differences in basic practices, and have become increasingly expensive – not the least because of all the necessary safeguards mandated by institutional review boards and ethics committees and of course the European Union Statutory Instruments, beginning with European Directive 2001/20/EC. Due to the multiple challenges and frustrations involved – ranging from bureaucracy to the difficulty of obtaining ethical permits – conducting this type of research is frequently a thankless job. Young medical researchers today must carefully consider how to reach their goal of becoming a successful clinical academic. As a rule, well-planned laboratory research promises speedy enough success, and with it, the steps to an academic career can be more precisely planned. A translational or laboratory research project usually lasts for a specified period of 2–3 years, can be financed through realistic grant awards, and usually concludes with at least one publication. In contrast, for a young researcher considering clinical trials as a pathway to academic advancement, the task seems almost impossible. A good multicenter, randomized clinical trial normally requires 2 or more years of planning, 2 to 6 years of implementation, and then 1 to 2 years of analysis before publication. If a similar career goal can be reached in a much shorter time, a young medical researcher is very unlikely to choose the clinical trial career pathway, with the necessity of enduring some 6-10 years of concentrated effort for a single publication. Let's take for example surgical oncology. The results of a good research project in translational oncology or molecular biology conducted by a recognized laboratory research group might be published in a journal like *Cancer Research* (impact factor >8), and a randomized controlled trial in the area of oncological surgery, method A versus method B, might be published in the *Annals of Surgery* (impact factor >7), the highest ranked surgical journal. In the curriculum vitae of an applicant for a professorship, these two publications might appear to have equal weight. But they are not of equal value, either in terms of the time and effort involved in achieving the output (publication), or in what ultimately matters—the impact on clinical practice. Thus, for clinical studies, a multiplication factor needs to be considered, which can be used together with a base value (for example, the impact factor of a journal) to assign a score to the particular study. In addition, the demands on social competency needed by a researcher conducting a multicenter randomized controlled trial – including motivating the teams involved and standardization of different local practices – support a multiplication factor of 5 in comparison to laboratory-based work, where the levels of coordination and standardization required are

much less.. In order to support the reorientation of young medical researchers toward clinical trials, a multiplication factor of 5-10, depending on the quality and complexity of the study, would seem to be justifiable. Patient advocacy organizations and politicians continue to call for more clinical evidence in medicine. Unless we change the system of evaluating research efforts, progress in clinical research will be considerably slower than it could and should be [001].

Coordinated research

The primary diseases of the pancreas include diabetes mellitus, acute and chronic pancreatitis, as well as pancreatic carcinoma. This review presents findings and emerging questions on the diseases of the pancreas obtained by the consortium of the Collaborative Research Center 518 (SFB 518), "Inflammation, Regeneration, and Transformation in the Pancreas" at the University of Ulm. During the last 12 years, the SFB 518 contributed considerably to the understanding of the cellular and molecular basis of pancreatic diseases and established the basis for the development of new strategies for prevention and causal therapy for diabetes, pancreatitis, and pancreatic cancer [002].

PANCREATIC HISTORY

Johan Georg Wirsüng

Many centuries have passed, and much has been written about the controversial discovery of the pancreatic duct by Johann Georg Wirsüng. His brutal death was even more mysterious, the truth being almost certainly blown away in the alleys of Renaissance Padua. In November 1629, after studying anatomy in Paris and Altdorf, the German student Johann Georg Wirsüng moved to Padua, where he graduated on March 23, 1630, with a doctorate in Philosophy and Medicine. He was then selected by the Professor of Anatomy Johan Wesling for the position of prosector of Padua, a role he held for the rest of his life. The discovery of the pancreatic duct occurred on March 2, 1642, at San Francesco Hospital during the autopsy of Zuane Viaro Della Badia, a 30 year-old man who had been hanged the day before. Wirsüng was assisted by two students, Thomas Bartholin of Denmark and Moritz Hoffmann of Germany. Wirsüng recognized that his finding was important, but had no idea about the possible function of the duct itself. Essentially, until then, the multiple roles of the pancreas were not appreciated; indeed, the pancreas was thought to be a cushion for the stomach and a pad supporting the vessels. Wirsüng did not publish his discovery; instead, he personally engraved an anatomic drawing of the pancreatic duct on a copperplate entitling it: "Picture of a kind of duct with multiple small branches, recently observed in different human bodies by Jo. Georg Wirsüng, Doctor in Phil. and Med." Thereafter, using this copperplate, Wirsüng made at least 7 impressions that were sent to authoritative anatomists across Europe (including his former mentor, Professor Riolan) to obtain their opinions on the function of the duct and—at the same time—to ensure priority of his finding. As the story is told, Wirsüng and his students initially thought that chyle from the spleen was transferred into the pancreas. No connection with the spleen, however, was demonstrated, and so the fluid found within the duct was assumed to be an excretion produced in the pancreas. This description was the first to establish the role of the pancreas as an excretory gland. As stated in his letters to Riolan, Wirsüng confirmed his discovery in human adults, newborns, and fetuses. He also kept investigating the duct on several animal species, but never really came to a conclusion regarding the actual function of the pancreas. But from here, the story becomes even more intriguing. Johann Georg Wirsüng was shot to death on August 22, 1643, in front of his house in Padua, near Collegio Pratense and the Basilica of St Anthony

by a Flemish man named Jacques Cambier. In 1715, the famous anatomist Giambattista Morgagni wrote that Wirsung was murdered for private revenge of unknown motivation [003].

John Howard (1919-2011)

John Howard was the “Father of US Pancreatology”. He was present at the first meeting of the Pancreas Club in 1966 at Northwestern and in a way could be considered one of the founding members although the group was not solidified until Charles Frey and William Schiller began organizing the meetings in 1975. John tracked down Wirsung’s copper plate and the seven known imprints (look at the home page of the Pancreas Club) and then wrote the story of Wirsung in *Journal of American Colleges of Surgeons* in 1998. He visited Whipple’s childhood missionary home in Iran and he was at the Vatican Archives in search of Whipple’s signature after Whipple had saved the US Ambassador to the Vatican for FDR in 1938. He then wrote the exhaustive two volume treatise - *The Life and Times of Allen Oldfather Whipple*. In a letter to the Pancreas Club in October 5, 2007 John notes “It is a scholarly biography of the “Father of Pancreatic Surgery” and the influence of his wonderful mother on his character. Over a decade of preparation went into the two volume set of over 1000 pages.” Truly a remarkable treatise about the Father of Pancreatic Surgery by the Father of Pancreatology [from the homepage of American Pancreas Club].

However it was his book *Surgical Diseases of the Pancreas* with George Jordan that began the evolution of the science of pancreatology in 1960, a time when little was known of this mysterious gland whose duct was first described long ago by Johann Wirsung in 1652 yet our knowledge did not begin to mature until long after insulin was first isolated in 1921. The latter was made possible by a surgeon’s knowledge (Banting) that the exocrine enzymes were interfering with the isolation process of the illusive hormone and ligating the blood supply to the pancreas would atrophy the gland. Subsequently, during this first part of the 20th Century, little else was known about the exocrine pancreas. Perhaps that was why John was attracted to this retroperitoneal organ. To quote Charlie Frey:

“John in 1960 published the first comprehensive textbook on pancreatic disease with his co-author George Jordan. Better than anyone had previously, he described and differentiated the natural history of Gallstone and Alcoholic pancreatitis. That book was the bible on the pancreas and the most influential text on the pancreas for about 20 years. I met John at the American Surgical Association meeting in 1964 when I was giving a paper with Frank Glenn, Chairman of Surgery at Cornell-New York Hospital on the operative management of Gallstone pancreatitis. John and I have been seeing each other at Surgical meetings ever since.”

In 2007 John had published 464 journal articles, book chapters and books – just 43 percent were on the pancreas – but to understand the evolution of pancreatology one must read the books of John Howard – these include the 3 very different editions of *Surgical Diseases of the Pancreas*, 1960, 1986, and 1998, the *History of the Pancreas. Mysteries of a Hidden Organ*, 2002, and the 2 volume treatise - *The Life and Times of Allen O. Whipple*, 2009 [from the homepage of American Pancreas Club].

John died peacefully after a very short (1 week) illness with CHF. He was 92. He was lucid until the day before his death, and actively participated in the decision to enter hospice (he was "enrolled" in hospice for about 2 days). He is survived by his second wife, former college sweetheart Sarah, as well as a large family [from the homepage of American Pancreas Club].

John. Howard arrived at the Medical College of Ohio, UTMC's predecessor, in 1973. He retired from surgery in 1993 but continued his research, teaching, and writing of journal

articles at the institution. Dr. Jeffrey Gold, the university's chancellor and executive vice president of health affairs, described him as "a prominent long-term member of the senior faculty of the department of surgery. He was a highly regarded biliary and pancreatic surgeon, and a world-renowned trauma surgeon. ... He was an author, a benefactor, and a friend of the university." Dr. Howard was a past director of the trauma center and a professor of surgery. As a young Army surgeon, Dr. Howard served in a Mobile Army Surgical Hospital during the Korean War and directed the Army's Surgical Research Team, which developed a method of repairing injured blood vessels in the field hospital "instead of tying them off and amputating the leg," Dr. Hussain said. The Army surgical team also established a renal care center that received all United Nations casualties with acute renal failure, the first time that had been done in combat medicine. President Dwight D. Eisenhower presented Dr. Howard with the Legion of Merit for his accomplishments during the Korean War. After his discharge from the Army, Dr. Howard joined the surgical faculty at Baylor University College of Medicine, where the director was famed heart surgeon Michael DeBakey. There, he put together a four-volume archive on the injuries and care wounded UN soldiers received in Korea. He went on to chair the departments of surgery at Emory University College of Medicine and Hahnemann University College of Medicine before arriving in Toledo. Over the years, he wrote more than 400 journal articles and wrote or contributed to 12 books and 31 book chapters. He was the recipient of awards from the National Research Council, the American Trauma Society, the American Medical Association, and the Toledo Surgical Society. The US Department of Transportation presented him with an award for "providing the vision that has become our nation's Emergency Medical Services." Dr. Howard was born in Prattville, Ala., the third of Mary and Fountaine Howard's four children. He grew up on a farm where he picked cotton and pecans. He and his first wife, Nina, were married for 57 years, until her death in 2000. In 2002, he married Sarah Shepherd Rice, whom he had known in college and reconnected with after many years. Surviving are his wife, Sarah; daughters, Nina Oakley, Susan Howard, and Laura Hickey; sons, John Jr., Robert, and George; sister, Mary Louise Jones, and 10 grandchildren and six great-grandchildren [from the Toledo Blade].

EMBRYOLOGY

Mouse embryonic stem cells (ESCs) can be induced to form pancreatic exocrine enzyme-producing cells in vitro in a stepwise fashion that recapitulates the development in vivo. However, there is no protocol for the differentiation of pancreatic-like cells from human ESCs (hESCs). Based upon the mouse ESC model, we have induced the in vitro formation of pancreatic exocrine enzyme-producing cells from hESCs. The protocol took place in four stages. In Stage 1, embryoid bodies (EBs) were formed from dissociated hESCs and then treated with the growth factor activin A, which promoted the expression of *Foxa2* and *Sox17* mRNAs, markers of definitive endoderm. In Stage 2, the cells were treated with all-trans retinoic acid which promoted the transition to cells that expressed gut tube endoderm mRNA marker *HNF1b*. In Stage 3, the cells were treated with fibroblast growth factor 7 (FGF7), which induced expression of *Pdx1* typical of pancreatic progenitor cells. In Stage 4, treatment with FGF7, glucagon-like peptide 1, and nicotinamide induced the expression *amylase (AMY)* mRNA, a marker for mature pancreatic exocrine cells. Immunohistochemical staining showed the expression of AMY protein at the edges of cell clusters. These cells also expressed other exocrine secretory proteins including elastase, carboxypeptidase A, chymotrypsin, and pancreatic lipase in culture. Production of these hESC-derived pancreatic enzyme-producing cells represents a critical step in the study of pancreatic organogenesis and in the development of a renewable source of human pancreatic-like exocrine cells [004].

ANATOMY AND ANOMALIES

Mesopancreas?

A recently published study hypothesized the concept of “mesopancreas”, defining it as a firm, well-vascularized structure extending from the posterior surface of the pancreatic head to behind the mesenteric vessels. They drew a parallel with mesorectum and suggested that resection of the mesopancreas may be as beneficial as in cases of total mesorectal excision in carcinoma of the rectum. The concept of mesopancreas prompts one very basic sceptical query, namely: does it have its enveloping fascias which can be demonstrated by dissection and or histopathology, which will allow the development of a dissection plane for its total extirpation? It stands to reason that, unless the mesopancreas is enveloped by a fascia covering the pancreas, it is not possible to label the pancreatic head and mesopancreas as one distinct lymphovascular entity, and its “en-block” excision is not possible. As no anatomical textbook mentions the presence of mesopancreas, one anatomical-pathological study was designed to verify and define mesopancreas from resection specimens obtained from fresh cadavers. Twenty fresh adult cadavers without any intra-abdominal injury or gross intra-abdominal pathology were investigated. Specimens containing the entire duodenum, pancreatic head and neck, gallbladder, cystic duct, common bile duct, superior mesenteric vessels, inferior vena cava and aorta were removed en-bloc. On gross examination, loose connective tissue, fat, peripheral nerves and small blood vessels were found between the head and neck of the pancreas, and the superior mesenteric artery and superior mesenteric vein. These were mainly concentrated between the head of the pancreas and the inferior vena cava (lateral to superior mesenteric vein). No fascia or fibrous layer was found enveloping these structures. The superior mesenteric vein and superior mesenteric artery were found in very close proximity (separated only by the fascia of Trietz) to the back of the pancreas and required a plane to be developed between the pancreas and the superior mesenteric vein and artery. Once this plane was developed, any distance measured would be artificially created distance and hence a false measurement, forcing us to abandon our efforts to measure the distance between the pancreas and the superior mesenteric vein and artery. Microscopic examination revealed loose areolar tissue, adipose tissue, peripheral nerve, nerve plexus, lymphatics and capillaries. All these structures were found just behind the pancreatic head and neck, extending between the neck of the pancreas and the uncinate process of the pancreas to the superior mesenteric artery and the superior mesenteric vein, and from the head of the pancreas to the inferior vena cava. Lymphatics were found up to the aorto-caval groove. No fibrous sheath or fascia was found around these structures, even on microscopy. In the study, no fascia or fibrous layer was found, neither macroscopically or microscopically, enveloping retropancreatic loose areolar tissue containing adipose tissue, peripheral nerves, nerve plexus, lymphatics and capillaries, even on microscopy, making it impossible to remove the mesopancreas with the head of the pancreas ‘en-bloc’ in a standardized manner. Inversely to the simplicity of rectal embryology, the tissues located at the posterior surface of the head of the pancreas represent a site of embryologic fusion of peritoneal layers called the Treitz’s fusion fascia. The complexity of the vascular, lymphatic and nervous network in the retropancreatic area is not surrounded by a real “meso”, making it impossible to totally remove and ‘en-bloc’ during a pancreaticoduodenectomy for cancer. The hypothesis of mesopancreas, although anatomically unfounded, reflects the ongoing attention given to the retropancreatic margin of clearance in a pancreaticoduodenectomy for carcinoma of the pancreas. The importance of the retropancreatic margin is further evidenced by attempts to standardize its mapping and description by pathologists. However, loose areolar tissue, adipose tissue, peripheral nerve, nerve plexus, lymphatics and capillaries are found in retropancreatic tissue, extending between the head, neck and uncinate process of the pancreas to the aorto-caval groove. There is no envelope of fibrous sheath or fascia around these structures, similar to the mesorectum. The presence of vessels, nerves and lymphatics within the retroperitoneal adipose tissue is not sufficient to

justify the identification of these structures as a true “meso” since the two peritoneal leaves encircling the vessels and linked with the parietal peritoneum are not present. Neither is there a “holy plane” of dissection, ensuring its complete and easy removal. Hence, it can be concluded that the concept of ‘mesopancreas’ is a myth, and the name a misnomer [005].

Pancreatic arteries

The aim of surgery for carcinoma of the pancreas is local complete resection of the carcinoma. All of the important pancreaticoduodenal arcades of arteries, veins, and nerves are situated on the fusion fascia of Treitz. The pancreatic parenchyma, extrapancreatic nerve plexuses, superior mesenteric artery (SMA), and portal vein are also covered within the fusion fascia and exist in the same area. Carcinoma of the head of the pancreas invades through the pancreatic parenchyma, following the arteries, veins, and especially nerves between the parenchyma and fusion fascia, and then spreads horizontally toward the SMA or celiac axis. The entire dissected end of the nerve plexus should be investigated during surgery using frozen specimens and confirmed to be negative for cancer. If the dissected end is positive for cancer, additional resection of the nerve plexus should be performed to achieve curative resection. It is not possible to investigate thoroughly whether the dissected end of the nerve plexus is positive or negative for carcinoma after surgery, since the end may be long and some specimens may be deformed by formalin fixation; thus it is difficult to identify the true surgically dissected end. The pancreaticoduodenal artery arises from the left side of the SMA and divides into two arteries: jejunal artery 1; and the inferior pancreaticoduodenal artery (IPDA), which runs behind and transversely to the right of both the anterior and posterior IPDA. A common origin of the anterior and posterior IPDA is found in 80 percent of cases. The postoperative course of patients with pancreatic head carcinoma with invasion of the perineural plexuses immediately behind the SMA is not as good as in that of patients without cancerous invasion, even if additional resection is performed so that the dissected end is confirmed to be negative during surgery. Nevertheless, intraoperative pathologic examination of the entire dissected end of the neural plexus remains necessary for curative R0 resection [006].

Intrapancreatic fat

One study was aimed to establish a database of pancreatic fat fractions for healthy men aged 20 to 70 years using double-echo chemical shift gradient-echo magnetic resonance imaging. The double-echo chemical shift gradient-echo magnetic resonance imaging technique was used in this study. A phantom of fat-water mixtures was established to test the accuracy of the sequence. In addition, 126 healthy male volunteers (20-70 years, body mass index ≤ 25) were enrolled. Fat content of the pancreas (head, body, and tail) was examined. On the phantom, a significant positive linear correlation and linear regression was found between the calculated and actual fat fractions of fat emulsions. For volunteers, there was no significant difference regarding fat fractions among the 3 regions of pancreata in each age group. Pancreatic fat fraction ($6\% \pm 1\%$) of healthy men aged 50 to 70 years was approximately 1-fold higher than that ($3\% \pm 1\%$) of those aged 20 to 50 years. It was concluded that double-echo chemical shift gradient-echo magnetic resonance imaging is useful for quantifying pancreatic fat fraction. This noninvasive technique has revealed an even distribution of pancreatic fat in healthy men, aging as an independent risk factor for pancreatic steatosis, and the increase in pancreatic fat fraction beginning in the fifth decade [007].

Portal vein aneurysm

Primary portal venous aneurysms are rare; however, they are the most common visceral venous aneurysms, and their pathogenesis is not fully understood. Complications include thrombosis, rupture, and mass effect on adjacent structures. The optimal management of these patients is not known. It was described a patient whose large (6 cm) portal vein aneurysm underwent complete spontaneous regression over several years of serial observation [008].

Polysplenia

Polysplenia, as part of the heterotaxy syndrome, is a rare embryological disorder which results from failure of development of the usual left-right asymmetry of organs. It is often associated with cardiac and biliary abnormalities, which are the usual causes of death in early neonatal life. A congenitally short pancreas and abnormalities with portal vein formation, gut malrotations and inferior vena cava anomalies are known to be associated with this rare syndrome. It was reported a case of polysplenia in an adult female presenting with obstructive jaundice owing to choledocholithiasis, possibly formed by biliary stasis as a result of compression of the common bile duct by the preduodenal portal vein, and review the literature. The patient was also found to have complete agenesis of the dorsal pancreas on CT and endoscopic retrograde cholangiopancreatography [009].

Ectopic pancreas

Although ectopic pancreas and intussusception are not unusual conditions, intussusception caused by ectopic pancreas is extremely rare. Its presence along with a ruptured congenital mesenteric vascular band raises the possibility of an anomaly of the vitelline vascular system. We report the case of a 26-year-old man presenting with acute abdominal pain, vomiting, and diarrhea. CT scan showed a large amount of free fluid in his abdomen and an ileo-ileal intussusception. At laparotomy he was found to have hemoperitoneum with a ruptured, actively bleeding congenital band attached to the ileal mesentery, which was ligated, with ileo-ileal intussusception that was resected. Histopathology showed ectopic pancreatic tissue as the lead point for the intussusception. It was likely to be a ruptured mesodiverticular band and along with other findings suggested a constellation of anomalies of the vitello-intestinal tract [010].

PHYSIOLOGY

Chymotrypsin C

Human digestive carboxypeptidases CPA1, CPA2, and CPB1 are secreted by the pancreas as inactive proenzymes containing a 94-96-amino acid-long propeptide. Activation of procarboxypeptidases is initiated by proteolytic cleavage at the C-terminal end of the propeptide by trypsin. Here, it was demonstrated that subsequent cleavage of the propeptide by chymotrypsin C (CTRC) induces a nearly 10-fold increase in the activity of trypsin-activated CPA1 and CPA2, whereas CPB1 activity is unaffected. Other human pancreatic proteases such as chymotrypsin B1, chymotrypsin B2, chymotrypsin-like enzyme-1, elastase 2A, elastase 3A, or elastase 3B are inactive or markedly less effective at promoting procarboxypeptidase activation. On the basis of these observations, we propose that CTRC

is a physiological co-activator of proCPA1 and proCPA2. Furthermore, the results confirm and extend the notion that CTSC is a key regulator of digestive zymogen activation [011].

Pancreatic lipase-related protein-2

In newborn mice, PLRP2 is essential for fat digestion. In human infants, the role of PLRP2 in fat digestion is unclear, as it has poor activity against long-chain triglycerides in vitro. Also, many infants carry a genetic polymorphism resulting in a truncated protein, PLRP2 W340X, which may impact function significantly. It was therefore re-examined the properties of recombinant human PLRP2 and studied the impact of W340X mutation on its function. In the presence of bile salt micelles and colipase, human PLRP2 hydrolyzed long-chain tri-, di-, and monoglycerides. It hydrolyzed triolein at a level much lower than that of pancreatic triglyceride lipase, but close to that of carboxyl ester lipase, after a long lag phase, which could be eliminated by the addition of oleic acids. Human PLRP2 W340X was poorly secreted and largely retained inside the cell. The retention of the mutant protein triggered endoplasmic reticulum stress and unfolded protein responses. Our results show that earlier studies underestimated human PLRP2 activity against triolein by employing suboptimal assay conditions. In vivo, dietary fat emulsions contain fatty acids as a result of the action of gastric lipase. Consequently, PLRP2 can contribute to fat digestion during early infancy. Furthermore, infants with homozygous W340X alleles will not secrete functional PLRP2 and may have inefficient dietary fat digestion, particularly when breastfeeding is unavailable. Additionally, the aberrant folding of W340X mutant may cause chronic cellular stress and increase susceptibility of pancreatic exocrine cells to other metabolic stressors [012].

DIABETES MELLITUS TYPE I AND II

Overview

Present knowledge on pathogenic mechanisms in type 1 and type 2 diabetes mellitus may offer the identical scheme of the cascade steps disturbing B-cell and its organelles. The only one difference is based in the initiation of the whole cascade by cytokines activated in previous infection (Type 1 DM) or by increased concentration of free fatty acids (Type 2 DM) in the individuals with different genetic background for both types of diabetes. Impaired function and structure of mitochondria causes cell failure and its following apoptosis. The elucidation of the cause of changes in developed diabetes enables to suggest some perspective therapeutic approaches and/or preventive ways [013].

Insulin

Insulin resistance is the most important pathophysiological feature in many pre-diabetic states. Type 2 diabetes mellitus is a complex metabolic disease and its pathogenesis involves abnormalities in both peripheral insulin action and insulin secretion by pancreatic beta cells. The creation of monogenic or polygenic genetically manipulated mice models in a tissue-specific manner was of great help to elucidate the tissue-specificity of insulin action and its contribution to the overall insulin resistance. However, complete understanding of the molecular bases of the insulin action and resistance requires the identification of the intracellular pathways that regulate insulin-stimulated proliferation, differentiation and metabolism. Accordingly, cell lines derived from insulin target tissues such as brown adipose tissue, liver and beta islets lacking insulin receptors or sensitive candidate genes such as IRS-1, IRS-2, IRS-3, IR and PTP1B were developed. Indeed, these cell lines have been also very useful to understand the tissue-specificity of insulin action and inaction [014].

Incretins

Antidiabetic therapies based on potentiation of incretin action are now widely used; however, understanding of their long-term safety remains incomplete. It was searched articles in PubMed for data assessing the safety of incretin-based therapies. Three major areas of interest are reviewed: incretin action in the cardiovascular system, pancreatitis, and cancer. Incretin therapies reduce weight gain, minimize hypoglycemia, decrease inflammation, and are cardioprotective in preclinical studies. However, data permitting conclusions about whether incretin therapies modify the development of cardiovascular events in humans are not available. Case reports link incretin therapies to pancreatitis, but retrospective case control studies do not associate pancreatitis with glucagon-like peptide-1 receptor (GLP-1R) agonists or dipeptidyl peptidase-4 inhibitors. Preclinical studies of pancreatitis have yielded conflicting results, and mechanisms linking incretin receptor activation to pancreatic inflammation have not yet been forthcoming. GLP-1R activation promotes C-cell hyperplasia and medullary thyroid cancer in rodents; however, long-term clinical studies of sufficient size and duration to permit conclusions regarding cancer and incretin therapeutics have not yet been completed. The available data on incretin action and incidence of cardiovascular events, pancreatitis, or cancer are not yet sufficient or robust enough to permit firm conclusions regarding associations with incretin-based therapies in humans with diabetes. The forthcoming results of long-term cardiovascular safety studies should provide more conclusive information about the safety of GLP-1R agonists and dipeptidyl peptidase-4 inhibitors in diabetic patients [015].

Incretins including GLP-1 and GIP have pleiotropic effects on islet biology especially on beta-cell function. Not only enhancing glucose-stimulated insulin secretion, but incretins exert beta-cell mass maintaining effects by upregulation of proliferation and prevention of cell death (apoptosis). Recent research data revealed detailed molecular mechanisms underlying these effects of incretin on beta-cell biology. These beneficial effects of incretins on the regulation of beta-cell mass could contribute to future therapeutic approaches to diabetes focusing on preservation and upregulation of beta-cell mass as well as function [016].

Incretins, such as GIP and GLP-1 enhance insulin secretion from pancreatic beta cells in a glucose dependent manner. Incretins potentiate adenylate cyclase activity through their G-protein coupled receptors and then increase intracellular cAMP level. Intracellular cAMP modulates insulin secretion by both PKA-dependent and PKA-independent pathways. PKA potentiates intracellular Ca^{2+} influx via phosphorylation of voltage-dependent calcium channel (VDCC), which increases insulin exocytosis. PKA also phosphorylates K(ATP) channel and facilitates insulin release. In contrast, Epac2 potentiates insulin secretion by cAMP in a PKA-independent pathway. The small G-protein Rap1, which is activated specifically through Epac2, contributes the first phase of insulin secretion possibly by control of insulin granules fusion to plasma membrane [017].

Incretin hormones, GLP-1 and GIP, contribute to whole body glucose homeostasis by modulating secretion of islet hormones, insulin, glucagon and somatostatin. Both GLP-1 and GIP stimulate insulin and somatostatin secretion, whereas glucagon secretion is stimulated by GIP, and GLP-1 suppresses glucagon secretion. The mechanism by which GLP-1 suppresses glucagon secretion seems to include direct action of the hormone on alpha cells and indirect one through activation of beta and delta cells. However, molecular details of these actions still remain elusive [018].

The incretin hormones, glucose-dependent insulintropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1), which are secreted by cells of the gastrointestinal tract in response to meal ingestion, exercise important glucoregulatory effects, including the glucose-dependent potentiation of insulin secretion by pancreatic beta-cells. Research on the defective incretin

action in type 2 diabetes mellitus suggests that the observed loss of insulinotropic activity may be due primarily to a decreased responsiveness of beta-cells to GIP. GLP-1 does retain efficacy, albeit not at physiologic levels. Accordingly, augmentation of GLP-1 is a logical therapeutic strategy to ameliorate this deficiency, although the short metabolic half-life of the native hormone renders direct infusion impractical. GLP-1 receptor agonists that resist degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) and have protracted-action kinetics have been developed, and DPP-4 inhibitors that slow the enzymatic cleavage of native GLP-1 provide alternative approaches to enhancing incretin-mediated glucose control. However, GLP-1 receptor agonists and DPP-4 inhibitors are premised on highly divergent mechanisms of action. DPP-4 is ubiquitously expressed in many tissues and is involved in a wide range of physiologic processes in addition to its physiologic influence on incretin hormone biological activity. GLP-1 receptor agonists provide a pharmacologic level of GLP-1 receptor stimulation, whereas DPP-4 inhibitors appear to increase levels of circulating GLP-1 to within the physiologic range. One article examined the physiology of the incretin system, mechanistic differences between GLP-1 receptor agonists and DPP-4 inhibitors used as glucose-lowering agents in the treatment of type 2 diabetes, and the implications of these differences for treatment. The results of recent head-to-head trials were reviewed, comparing the effects of incretin-based therapies on a range of clinical parameters, including glycemia, beta-cell function, weight, and cardiovascular function [019].

Single GLP-1

To investigate the effect of exogenous as well as endogenous glucagon-like peptide 1 (GLP-1) on postprandial glucose excursions and to characterize the secretion of incretin hormones in type 1 diabetic patients with and without residual beta-cell function 8 type 1 diabetic patients with (T1D+), eight without (T1D-) residual beta-cell function, and eight healthy matched control subjects were studied during a mixed meal with concomitant infusion of GLP-1 (1.2 pmol/kg/min), saline, or exendin 9-39 (300 pmol/kg/min). Before the meal, half dose of usual fast-acting insulin was injected. Plasma glucose (PG), glucagon, C-peptide, total GLP-1, intact glucose-dependent insulinotropic polypeptide (GIP), free fatty acids, triglycerides, and gastric emptying rate (GE) by plasma acetaminophen were measured. Incretin responses did not differ between patients and control subjects. Infusion of GLP-1 decreased peak PG by 45 percent in both groups of type 1 diabetic patients. In T1D+ patients, postprandial PG decreased below fasting levels and was indistinguishable from control subjects infused with saline. In T1D- patients, postprandial PG remained at fasting levels. GLP-1 infusion reduced GE and glucagon levels in all groups and increased fasting C-peptide in T1D+ patients and control subjects. Blocking endogenous GLP-1 receptor action increased endogenous GLP-1 secretion in all groups and increased postprandial glucose, glucagon, and GE in T1D+ and T1D- patients. The insulinogenic index (the ratio of insulin to glucose) decreased in T1D+ patients during blockade of endogenous GLP-1 receptor action. It was concluded that in type 1 diabetic patients have normal incretin responses to meals. In type 1 diabetic patients, exogenous GLP-1 decreases peak postprandial glucose by 45% regardless of residual β -cell function. Endogenous GLP-1 regulates postprandial glucose excursions by modulating glucagon levels, GE, and beta-cell responsiveness to glucose. Long-term effects of GLP-1 in type 1 diabetic patients should be investigated in future clinical trials [020].

Islet amyloid polypeptide

A 37-residue of human islet amyloid polypeptide (hIAPP or amylin) is a main component of amyloid plaques found in the pancreas of about 90 percent of type II diabetes patients. It is reported that hIAPP oligomers, rather than mature fibrils, are major toxic species responsible

for pancreatic islet beta-cell dysfunction and even cell death, but molecular structures of these oligomers remain elusive. In one work, on the basis of recent solid-state NMR and mass-per-length (MPL) data, it was modeled a series of hIAPP oligomers with different beta-layers (one, two, and three layers), symmetries (symmetry and asymmetry), and associated interfaces using molecular dynamics simulations. Three distinct interfaces formed by C-terminal beta-sheet and C-terminal beta-sheet (CC), N-terminal beta-sheet and N-terminal beta-sheet (NN), and C-terminal beta-sheet and N-terminal beta-sheet (CN) are identified to drive multiple cross- β -layers laterally associated together to form different amyloid organizations via different intermolecular interactions, in which the CC interface is dominated by polar interactions, the NN interface is dominated by hydrophobic interactions, and the CN interface is dominated by mixed polar and hydrophobic interactions. Overall, the structural stability of the proposed hIAPP oligomers is a result of delicate balance between maximization of favorable peptide-peptide interactions at the interfaces and optimization of solvation energy with globular structure. Different hIAPP oligomeric models indicate a general and intrinsic nature of amyloid polymorphism, driven by different interfacial side-chain interactions. The proposed models are compatible with recent experimental data in overall size, cross-section area, and molecular weight. A general hIAPP aggregation mechanism is proposed on the basis of the simulated models and experimental data [021].

Islet amyloid polypeptide (IAPP, or amylin) is one of the major secretory products of beta-cells of the pancreatic islets of Langerhans. It is a regulatory peptide with putative function both locally in the islets, where it inhibits insulin and glucagon secretion, and at distant targets. It has binding sites in the brain, possibly contributing also to satiety regulation and inhibits gastric emptying. Effects on several other organs have also been described. IAPP was discovered through its ability to aggregate into pancreatic islet amyloid deposits, which are seen particularly in association with type 2 diabetes in humans and with diabetes in a few other mammalian species, especially monkeys and cats. Aggregated IAPP has cytotoxic properties and is believed to be of critical importance for the loss of beta-cells in type 2 diabetes and also in pancreatic islets transplanted into individuals with type 1 diabetes. One review dealt both with physiological aspects of IAPP and with the pathophysiological role of aggregated forms of IAPP, including mechanisms whereby human IAPP forms toxic aggregates and amyloid fibrils [022].

Pancreatic volume in diabetes

Exocrine function has been described in patients with diabetes. It was hypothesized that patients with exocrine dysfunction have pancreatic atrophy in a cohort study of hospitalized patients. Thirty-five patients were selected after detection of impaired exocrine function in routine tests, and 17 patients were matched for age and body mass index to the previous cohort. The pancreatic volume was evaluated on sections of computed tomographic scans of the pancreas. Other investigations included a glucagon stimulation test and determination of fecal elastase-1 concentration and chymotrypsin activity. Fifty-two patients participated in the study, 24 with type 1 diabetes and 28 with type 2 diabetes. Duration of diabetes was 15 years (5-26 years; median, interquartile range). The pancreatic volume, 42 cm³ (25-57 cm³), was decreased in most patients. It did not differ in patients with type 1 diabetes compared with those with type 2 diabetes. It was decreased in patients treated with insulin and in those with low elastase-1 concentration or low chymotrypsin activity. In the multiple linear regression analysis, the pancreatic volume correlated with chymotrypsin activity and stimulated C-peptide. It was thus unraveled a link between 2 old observations in patients with diabetes: atrophy of the pancreas and exocrine deficiency. These observations give credence to the reality of the exocrine dysfunction in patients with diabetes [023].

Genetics in diabetes

Type 1 diabetes, a multifactorial disease with a strong genetic component, is caused by the autoimmune destruction of pancreatic beta-cells. The major susceptibility locus maps to the HLA class II genes at 6p21, although more than 40 non-HLA susceptibility gene markers have been confirmed. Although HLA class II alleles account for up to 30-50 percent of genetic type 1 diabetes risk, multiple non-MHC loci contribute to disease risk with smaller effects. These include the insulin, PTPN22, CTLA4, IL2RA, IFIH1, and other recently discovered loci. Genomewide association studies performed with high-density single-nucleotide-polymorphism genotyping platforms have provided evidence for a number of novel loci, although fine mapping and characterization of these new regions remain to be performed. Children born with the high-risk genotype HLADR3/4-DQ8 comprise almost 50 percent of children who develop antiislet autoimmunity by the age of 5 years. Genetic risk for type 1 diabetes can be further stratified by selection of children with susceptible genotypes at other diabetes genes, by selection of children with a multiple family history of diabetes, and/or by selection of relatives that are HLA identical to the proband. Thus, children with the HLA-risk genotypes DR3/4-DQ8 or DR4/DR4 who have a family history of type 1 diabetes have more than a 1 in 5 risk for developing islet autoantibodies during childhood, and children with the same HLA-risk genotype but no family history have approximately a 1 in 20 risk. Determining extreme genetic risk is a prerequisite for the implementation of primary prevention trials, which are now underway for relatives of individuals with type 1 diabetes [024].

Cell-based therapies

Diabetes affects 246 million people around the world. To date, no definitive cure has been discovered. Recent clinical trials have shed light on the possibility of successfully transplanting adult pancreatic islets into type 1 diabetic recipients. However, despite encouraging efforts to improve such protocols, the poor availability of pancreatic islets remains a limiting parameter for these transplantation programmes. In one review, different strategies to obtain other sources of islet beta cells were discussed [025].

Carboxyl ester lipase gene-maturity onset diabetes of the young (CEL-MODY)

CEL-maturity onset diabetes of the young (MODY), diabetes with pancreatic lipomatosis and exocrine dysfunction, is due to dominant frameshift mutations in the acinar cell carboxyl ester lipase gene (CEL). As Cel knock-out mice do not express the phenotype and the mutant protein has an altered and intrinsically disordered tandem repeat domain, we hypothesized that the disease mechanism might involve a negative effect of the mutant protein. In silico analysis showed that the pI of the tandem repeat was markedly increased from pH 3.3 in wild-type (WT) to 11.8 in mutant (MUT) human CEL. By stably overexpressing CEL-WT and CEL-MUT in HEK293 cells, it was found similar glycosylation, ubiquitination, constitutive secretion, and quality control of the two proteins. The CEL-MUT protein demonstrated, however, a high propensity to form aggregates found intracellularly and extracellularly. Different physicochemical properties of the intrinsically disordered tandem repeat domains of WT and MUT proteins may contribute to different short and long range interactions with the globular core domain and other macromolecules, including cell membranes. Thus, it was proposed that CEL-MODY is a protein misfolding disease caused by a negative gain-of-function effect of the mutant proteins in pancreatic tissues [026].

Effect of gastric by-pass surgery

The effects of various weight loss strategies on pancreatic beta cell function remain unclear. It was aimed to compare the effect of intensive lifestyle intervention (ILI) and Roux-en-Y gastric bypass surgery (RYGB) on beta cell function. One hundred and nineteen morbidly obese participants without known diabetes from the MOBIL study (median body mass index (BMI) 46, 84 women) were allocated to RYGB (n=64) or ILI (n=55). The patients underwent repeated oral glucose tolerance tests (OGTTs) and were categorised as having either normal (NGT) or abnormal glucose tolerance (AGT). Twenty-nine normal-weight subjects with NGT served as controls. OGTT-based indices of beta cell function were calculated. One year weight reduction was 30 percent after RYGB and 9 percent after ILI, which was a significant difference. Disposition index (DI) increased in all treatment groups, although more in the surgery groups. Stimulated proinsulin-to-insulin ratio decreased in both surgery groups but to a greater extent in the surgery group with AGT at baseline. Post surgery, patients with NGT at baseline had higher DI and lower stimulated proinsulin to insulin ratio than controls. Gastric bypass surgery improved beta cell function to a significantly greater extent than intensive lifestyle intervention. Supra-physiological insulin secretion and proinsulin processing may indicate excessive beta cell function after gastric bypass surgery [027].

Cannabinoids in diabetes

Optimal glucose homeostasis requires exquisitely precise adaptation of the number of insulin-secreting beta-cells in the islets of Langerhans. Insulin itself positively regulates beta-cell proliferation in an autocrine manner through the insulin receptor (IR) signaling pathway. It is now coming to light that cannabinoid 1 receptor (CB1R) agonism/antagonism influences insulin action in insulin-sensitive tissues. However, the cells on which the CB1Rs are expressed and their function in islets have not been firmly established. We undertook the current study to investigate if intraislet endogenous cannabinoids (ECs) regulate beta-cell proliferation and if they influence insulin action. It was measured EC production in isolated human and mouse islets and beta-cell line in response to glucose and KCl. ECs are generated within beta-cells, which also express CB1Rs that are fully functioning when activated by ligands. Genetic and pharmacologic blockade of CB1R results in enhanced IR signaling through the insulin receptor substrate 2-AKT pathway in beta-cells and leads to increased beta-cell proliferation and mass. CB1R antagonism in db/db mice results in reduced blood glucose and increased beta-cell proliferation and mass, coupled with enhanced IR signaling in beta-cells. Furthermore, CB1R activation impedes insulin-stimulated IR autophosphorylation on beta-cells. These findings provide direct evidence for a functional interaction between CB1R and IR signaling involved in the regulation of beta-cell proliferation and will serve as a basis for developing new therapeutic interventions to enhance beta-cell function and proliferation in diabetes [028].

Nutrition in diabetes

One article summarized the Diabetes UK evidence-based guidelines for the prevention of Type 2 diabetes and nutritional management of diabetes. It describes the development of the recommendations and highlights the key changes from previous guidelines. The nutrition guidelines include a series of recommendations for the prevention of Type 2 diabetes, nutritional management of Type 1 and Type 2 diabetes, weight management, management of microvascular and macrovascular disease, hypoglycaemia management, and additional considerations such as nutrition support, end-of-life care, disorders of the pancreas, care of the older person with diabetes, nutrition provided by external agencies and fasting. The evidence-based recommendations were graded using the Scottish Intercollegiate Guidelines

Network methodology and, in a small number of topic areas, where strong evidence was lacking, the recommendations were reached by consensus. The Diabetes UK 2011 guidelines place an emphasis on carbohydrate management and a more flexible approach to weight loss, unlike previous guidelines which were expressed in terms of recommendations for individual nutrient intakes. Additionally, the guidelines for alcohol have been aligned to national recommendations. The full evidence-based nutrition guidelines for the prevention and management of diabetes are available from: <http://www.diabetes.org.uk/nutrition-guidelines> [029].

PANCREATOGENIC DIABETES (TYPE 3C)

Pancreatogenic, or type 3c, diabetes (T3cDM) occurs due to inherited or acquired pancreatic disease or resection. Although similar to the more prevalent type 1 and type 2 diabetes, pancreatogenic diabetes has a unique pattern of hormonal and metabolic characteristics. T3cDM accounts for 5-10 percent of Western diabetic populations and is associated with mild to severe disease. Recent findings on the pathophysiology of pancreatogenic diabetes have revealed that it is a form of diabetes with clinical and laboratory features which are distinct from both type 1 diabetes mellitus (T1DM) and T2DM, and its eventual course is impacted by a high risk for the development of pancreatic cancer in the majority of patients (75 %) whose diabetes is a consequence of chronic pancreatitis. In its extreme manifestation, the condition is difficult to treat because of a paradoxical combination of normal or enhanced peripheral insulin sensitivity and decreased hepatic insulin sensitivity. Patients become hyperglycemic because of unsuppressed hepatic glucose production (HGP), or become hypoglycemic when insulin replacement is barely excessive, as a result of the enhanced peripheral insulin sensitivity and a deficiency of pancreatic glucagon secretion [030].

Processes leading to diffuse destruction of the pancreas, such as pancreatic resection and chronic pancreatitis, result in pancreatic hormone deficiencies and altered responses of related organs to pancreatic hormones, thereby causing a type of impaired glucose metabolism known as pancreatogenic diabetes, T3cDM. Pancreatogenic diabetes after pancreatic resection differs from type 1 and type 2 diabetes mellitus. Unlike type 1 diabetes mellitus, which is caused by cellular mediated autoimmune destruction of beta-cells of the pancreas and carries a high risk of hyperglycemia and ketoacidosis, pancreatogenic diabetes seldom causes ketoacidosis or severe hyperglycemia. Pancreatogenic diabetes is also unlike type 2 diabetes mellitus, which is characterized by insulin resistance and relative insulin deficiency, because patients with pancreatic diabetes are sensitive to insulin. Because of the increased peripheral sensitivity to insulin and the reduced glucagon level in pancreatogenic diabetes, exogenous insulin administration frequently causes hypoglycemic attacks, characteristically called 'brittle' diabetes. Iatrogenic hypoglycemia occasionally leads to hospitalization, irreversible damage to the central nervous system or even death. Because glycemic control in these patients is clinically challenging, HbA1c is usually quite high and nephropathy, neuropathy, and retinopathy can develop as a result of long-term inappropriate therapy. There is no dispute that total pancreatectomy results in insulin-dependent pancreatogenic diabetes [4,6,8]. Other surgical procedures can result in the onset of diabetes mellitus, the rate of which appears to be related to progression of the underlying disease (reduction of islets cell reserve), duration of follow-up, extent of resection, and type of surgery [031].

Medical history

Animal models of pancreatogenic diabetes (pancreatectomy and chronic pancreatitis) were used by Von Mering and Minkowski in 1883 to establish the central role of the pancreas in glucose metabolism, and by Banting and Best in 1921 for the extraction of insulin and to demonstrate its gluoregulatory effects. By the mid-1980s, insulin deficiency and a compensatory increase in peripheral insulin sensitivity was well known to be a consequence of the loss of functional pancreatic parenchyma. However, the alterations in insulin action were poorly understood until the euglycemic clamp technique of Andres et al was used. The clamp studies documented a prompt and dramatic insulin-induced lowering of hepatic glucose production in normal dogs, similar to the effects seen in normal man. This isolated hepatic resistance to insulin has subsequently been shown to be uniformly present and characteristic of pancreatogenic diabetes in patients with pancreatic malignancy, pancreatic resection, chronic pancreatitis, and cystic fibrosis [030].

Glucose metabolism in pancreatic cancer

Altered glucose metabolism is the most common metabolic hallmark of malignancies. The authors tested the hypothesis that glucose metabolism gene variations affect clinical outcome in pancreatic cancer. The authors retrospectively genotyped 26 single nucleotide polymorphisms from 5 glucose metabolism genes in 154 patients with localized disease and validated the findings in 552 patients with different stages of pancreatic adenocarcinoma. Association between genotypes and overall survival (OS) was evaluated using multivariate Cox proportional hazard regression models with adjustment for clinical predictors. Glucokinase (GCK) IVS1 + 9652C > T and hexokinase 2 (HK2) N692N homozygous variants were significantly associated with reduced OS in the training set of 154 patients ($P < .001$). These associations were confirmed in the validation set of 552 patients and in the combined dataset of all 706 patients ($P \leq .001$). In addition, HK2 R844K variant K allele was significantly associated with a better survival in the validation set and the combined dataset. When data were further analyzed by disease stage, glutamine-fructose-6-phosphate transaminase (GFPT1) IVS14-3094T>C, HK2 N692N and R844K in patients with localized disease and GCK IVS1 + 9652C>T in patients with advanced disease were significant independent predictors for OS. Haplotype CGG of GPI and GCTATGG of HK2 were associated with better OS, respectively. It was concluded that the authors demonstrated that glucose metabolism gene polymorphisms affect clinical outcome in pancreatic cancer. These observations support a role of abnormal glucose metabolism in pancreatic carcinogenesis [032].

Pathophysiology

Insulin, which is secreted from beta cells distributed evenly throughout the pancreas, decreases the serum glucose concentration by suppressing hepatic gluconeogenesis and glycogenolysis and by facilitating hepatic glycogen synthesis. Nondiabetic patients had lower fasting serum insulin and reduced C-peptide secretion after pancreatic resection. An increase in both peripheral sensitivity to insulin and the insulin-binding capacity of red blood cells are observed in pancreatogenic diabetes. The opposite effect is observed for insulin resistance in type 2 diabetes mellitus. The consequence of increased sensitivity to insulin is severe hypoglycemic attacks after excessive administration of insulin. While a reduction in insulin secretion is also observed in type 1 diabetes mellitus, insulin-binding capacity and sensitivity are usually unchanged. Thus, the amount of insulin receptors is not simply enhanced by up-regulation secondary to stimulant deficiency. A clear explanation at the molecular level has yet to be obtained, although intestinal malabsorption of fat in patients

with pancreatic disease is thought to be responsible, as some studies show that adipocytes from rats fed a high fat diet bind less insulin than those from controls [030].

Glucagon

Glucagon-secreting alpha cells are located predominantly in the body and tail of the pancreas. During fasting in a healthy population, glucagon maintains adequate glucose production by hepatocytes through stimulation of glycogenolysis and gluconeogenesis that together function as counter-regulatory mechanisms to control hypoglycemia. Like insulin, pancreatectomy reduces the fasting glucagon concentration, which might compensate for the decrease in insulin secretion and partly help to avoid the occurrence of pancreatogenic diabetes. By comparison, the decrease in glucagon from fasting promotes a hypoglycemic state when patients have been administered only a slight excess of insulin. Under physiological conditions, glucagon secretion decreases following a glucose load, thereby avoiding hyperglycemia. In type 2 diabetes, however, the suppression of glucagon induced by glucose is frequently decreased and postprandial hyperglucagonemia is associated with hyperglycemia because of increased hepatic glucose production. Likewise, impaired glucose-induced glucagon suppression is observed in patients after pancreatic resection. With the unsuppressed glucagon secretion, the increased hepatic sensitivity to glucagon after pancreatic resection causes hyperglycemia in a state of insulin deficiency [030].

Pancreatic polypeptide (PP)

Pancreatic polypeptide (PP), a 36-amino-acid polypeptide, is localized to specific cells called PP cells, which are located mostly in the ventral pancreatic head and uncinate process. PP deficiency had been documented in chronic pancreatitis, pancreatic resection and cystic fibrosis. Bastidas et al were unable to show any effect of acute administration of bovine PP on glucose metabolism and insulin action in an animal model of chronic pancreatitis; however, Sun et al found that the prolonged administration of PP for hours or days resulted in a reversal of the hepatic resistance to insulin in dogs with CP. Seymour et al applied the isotopic glucose clamp method to study non-diabetic patients who had undergone various forms of pancreatic resection for trauma, and found that after proximal pancreatectomy, patients were deficient in PP and had measureable hepatic insulin resistance which was reversed after an 8-hour infusion of bovine PP. Similarly, Brunicardi et al studied diabetic and non-diabetic patients with chronic pancreatitis and found that an 8-hour infusion of PP reversed the hepatic resistance to insulin and significantly improved oral glucose tolerance in patients with impaired glucose tolerance and diabetes [030].

Another study of patients with low levels of plasma PP following pancreatic resection and chronic pancreatitis demonstrated that hepatic glucose production during insulin infusion was not suppressed as it was in controls. PP administration to patients with PP deficiency was shown to improve their hepatic response to insulin. Thus, PP deficiency is related to hyperglycemia resulting from unsuppressed glucose production and is characteristic of pancreatogenic diabetes. These findings show the potential reversibility of PP deficiency in the abnormal glucose metabolism seen after pancreatic resection. Livers harvested from rats with chronic pancreatitis demonstrated an impaired response to insulin during isolated in vitro perfusion compared to livers taken from control animals, and insulin-binding studies confirmed that hepatocyte insulin receptor (IR) availability was profoundly impaired in livers harvested from rats with chronic pancreatitis. Goldstein et al found that administration of PP for at least 2 h before liver harvest restored insulin's action to near normal during isolated hepatic perfusion, and this was accompanied by restoration of normal hepatocyte IR availability. Seymour et al were able to show that hepatic PP receptors were upregulated in the rat model of chronic pancreatitis, consistent with a deficiency in PP induced by the disease, but the delay in action of PP treatment in restoring insulin sensitivity implied that the reversal in IR availability was a transcriptional or translational process. Subsequently, this

group reported that hepatocyte IR gene expression was regulated, in part, by PP. Avoidance of surgical PP deficiency, by duodenum- and/or pancreas-sparing techniques, has been associated with a lower incidence of postoperative diabetes in patients with chronic pancreatitis and premalignant lesions of the pancreas. Aspelund et al found that new postoperative diabetes occurred in only 8 percent of patients within 3 years after either the Beger or Frey procedure, compared with 25% of patients after the Whipple procedure. Therefore, conservative approaches to pancreatic resection or combined drainage and excavation procedures (as opposed to more extensive resections) appear to preserve endocrine pancreatic function when they preserve the PP-rich uncinate process of the pancreas [031].

Multihormonal abnormalities

Therefore, T3cDM develops in the setting of both insulin deficiency and PP deficiency, and hepatic insulin resistance is, at least partially, a consequence of PP deficiency. Because PP is secreted predominantly by cells in the head of the pancreas, all patients undergoing proximal or total pancreatectomy are subsequently PP deficient, and half of all pancreaticoduodenectomy patients are diabetic postoperatively. PP deficiency alone is not sufficient for diabetes to occur, but PP deficiency has been shown to be associated with glucose intolerance and hepatic insulin resistance. The absence of glucagon-secreting ability in T3cDM creates the risk for severe hypoglycemia due to the loss of this counter-regulatory mechanism. Finally, the secretion of the enteric glucoregulatory hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP- 1) has been found to be impaired in patients with chronic pancreatitis. The combined multi-hormonal abnormalities of T3cDM due to pancreatitis therefore result in a severely perturbed endocrine environment which is, however, different than the pattern of abnormalities seen in either T1DM or T2DM [030].

Distal pancreatectomy

In the clinical setting, a euglycemic patient with obesity and subclinical impaired glucose tolerance might develop overt diabetes mellitus after pancreatic resection because of preoperative insulin resistance and relative insulin deficiency. Therefore, this patient possesses the characteristic hormonal and clinical features of type 2 diabetes mellitus and not necessarily those of pancreatogenic diabetes. Thus, in order to properly diagnose pancreatogenic diabetes mellitus after pancreatic resection, it is necessary to measure the levels of pancreatic hormones and the degree of insulin sensitivity. Distal pancreatectomy is the resection of the tail and body of the pancreas, which volume of resection depends on the location of the responsible disease. Hutchins et al studied 90 patients undergoing distal pancreatectomy for chronic pancreatitis with a mean follow-up period of 34 months. The median pancreatic resection volume was 50 percent (range 10-90 %) of the total volume. Of the 77 patients whose pancreatic endocrine functions were assessed, 7 had glucose intolerance, 8 had diabetes mellitus preoperatively, 18 (23 %) showed diabetes mellitus immediately after pancreatic resection, and another 14 developed "delayed" diabetes mellitus within a median period of 27 months from surgery to onset. Together with other clinical studies, these findings show that patients with chronic pancreatitis have a 25-50 percent risk of developing diabetes mellitus shortly after distal pancreatectomy. Malka et al prospectively studied 500 patients with chronic pancreatitis to elucidate risk factors associated with the onset of diabetes mellitus. Of these patients, 51 percent had undergone elective surgeries, such as pancreatic drainage, pancreatoduodenectomy and distal pancreatectomy, and the remaining 49 percent had not been operated on. The cumulative rate of the appearance of diabetes was 83 ± 4 percent at 25 years after the onset of chronic pancreatitis. Univariate and time-dependent multivariate analysis identified the onset of pancreatic calcification and

distal pancreatectomy as independent risk factors for diabetes mellitus and insulin dependency. However, the prevalence of diabetes mellitus did not increase in the surgical group overall, implying that the development of late-onset diabetes mellitus following pancreatic resection reflects the natural course of chronic pancreatitis rather than the operation itself. Compared with resection in treating chronic pancreatitis, resection of pancreatic tumors apparently has a lesser impact on endocrine function. A study of 235 patients with pancreatic diseases, including 23 percent with chronic pancreatitis and 77 percent with tumorous pancreatic disease, revealed the rate of new-onset diabetes mellitus after distal pancreatectomy to be approximately 8 percent. King et al reported a similar result in a study of 125 patients who had undergone distal pancreatectomy, mainly for pancreatic neoplastic lesions. In their study, only 9 percent of previously nondiabetic patients developed diabetes mellitus during a median follow-up period of 21 months. The rate of new-onset diabetes mellitus after distal pancreatic resection in patients with presumably normal pancreatic parenchyma is unexpectedly low at approximately 5-9 percent [031].

A key clinical observation is that preoperatively nondiabetic donors who undergo a hemipancreatectomy (a procedure similar to 50 percent distal pancreatectomy) to provide a hemi-pancreas for transplantation can develop diabetes mellitus or glucose intolerance. Kendall et al noted that 25 percent of healthy donors (7/28 donors) who provide a hemi-pancreas to a first-degree relative with type 1 diabetes mellitus develop impaired glucose tolerance within one year of the surgery. However, there was no obvious new-onset diabetes mellitus in these donors. A later study evaluated the glucose metabolic state of 21 donors from 3 to 10 years after they had undergone hemi-pancreatectomy for organ donation. Of the 15 donors located on follow-up, 2 had been taking an antidiabetic agent, and the remaining 13 underwent metabolic evaluation. Abnormalities in glucose metabolism were identified in 7 of the 13 patients including one with diabetes and 6 with impaired glucose tolerance and/or impaired fasting glucose. While the rate of latent abnormalities was as high as 40 percent (6/15), the rate of overt diabetes mellitus development was 20 percent (3/15) during long-term follow-up. These results imply that the overt manifestation of diabetes after distal pancreatectomy with presumably normal pancreatic parenchyma is lower than previously considered. However, it still has a significant influence on glucose metabolism during long-term follow-up [031].

For patients with chronic pancreatitis, the risk of diabetes mellitus shortly after distal pancreatectomy is 25-50 percent, and late-onset diabetes tends to be related to the clinical course of chronic pancreatitis. For patients with normal pancreatic parenchyma and tumorous lesions, the rate of diabetes mellitus is relatively low shortly after distal pancreatectomy. However, the risk of developing impaired glucose tolerance and/or impaired fasting glucose in hemi-pancreatectomized donors is high. Hence, the development of late-onset diabetes mellitus should be monitored in these patients [031].

Central pancreatectomy

Replication of beta-cells is an important mechanism of beta-cell expansion in early childhood. In obese or pregnant adult humans, the beta-cell mass is known to increase adaptively. However, in adulthood replication occurs to a considerably smaller extent, if at all. The capacity for beta-cell replication in humans is highest immediately after birth and then becomes markedly lower through adulthood. A recent study of 13 patients with a median age of 52 years demonstrated that a 50 percent pancreatectomy does not promote beta-cell regeneration. These findings explain the high incidence of impaired glucose metabolism after pancreatic resection and highlight the need for parenchyma sparing procedures. Central pancreatectomy, also called middle pancreatectomy, is the resection of the body segment of pancreatic parenchyma. Central pancreatectomy is utilized mostly for patients with small benign tumors located in the body of pancreas. While the proximal part of the remnant

pancreas is usually left without anastomosis, the distal part of the remnant pancreas requires anastomosis to the gastrointestinal tract in order to drain the pancreatic juice into the alimentary tract. Adham et al reported that following central pancreatectomy for benign tumors, none of the 50 patients in their study developed diabetes mellitus during the median follow-up period of 55 months. Other studies also demonstrated excellent long-term preservation of endocrine function. However, this complicated uncommon procedure is frequently associated with postoperative surgical complications. The incidence of pancreatic fistula, which can be fatal, is 5-30 percent after distal pancreatectomy and is theoretically higher after middle pancreatic resection since there are two possible sites of pancreatic fistula development. Pancreatic fistula may result in further destruction of islets cell mass due to inflammation itself and consequent stricture of the orifice of pancreatic duct to intestine, and the studies that compare the incidence of postoperative diabetes in those who develop pancreatic fistula and those who do not is required [031].

Proximal pancreatic resection (Whipple-like resections)

Proximal pancreatic resection is resection of the head of the pancreas. Duodenum-preserving pancreatic head resection avoids the resection of adjacent organs including duodenum, bile duct and gall bladder, which are commonly resected in "standard" pancreatoduodenectomy. Anastomosis of pancreatic duct of the remnant pancreas and gastrointestinal tract is necessary. Proximal pancreatic resection for chronic pancreatitis causes new-onset diabetes mellitus in 15-40 percent of patients. A comparison of endocrine functions revealed that duodenum-preserving pancreatic head resection is superior to the usual pancreatoduodenectomy procedure partly because the intestinal hormones are spared and a smaller amount of pancreatic parenchyma is resected. Beger et al reported on their 26 years of experience performing duodenum-preserving head resection for the treatment of painful, complicated chronic pancreatitis. This surgical treatment provided pain relief to 91 percent of patients. Of the 504 patients in the study, 303 had undergone glucose metabolic assessment within a median follow-up period of 6 years. The investigation identified 134 patients with insulin-dependent diabetes mellitus (44 %), 64 with new-onset insulin-dependent diabetes mellitus (21 %), 34 with improved metabolism, and 118 with normal oral glucose tolerance test results (39 %). For patients with benign or malignant tumors, data on the incidence of diabetes mellitus after pancreatoduodenectomy are more limited. Compared with chronic pancreatitis, fewer patients (18-27 %) with presumably normal pancreatic parenchyma develop diabetes mellitus after pancreatic resection for benign pancreatic tumors. Amelioration of the diabetic state has sometimes been observed after pancreatoduodenectomy for pancreatic cancer. Mechanisms speculated to underlie the improved glucose metabolism following surgery include the removal of factors secreted by the adenocarcinoma and/or inflammation due to obstructive lesions of the pancreas and delayed gastric emptying. Diabetogenic factors secreted by pancreatic tumors or local inflammation might alter glucose metabolism and cause insulin resistance; in this case, resection of the tumor can improve glucose metabolism. However, the diversity of measurement methods for insulin resistance has contributed to inconsistent findings among studies. Furthermore, improvement of the glycemic state commonly occurs after pancreatoduodenectomy and is rarely observed after distal pancreatectomy. Delayed gastric emptying or reduced caloric intake after pancreatoduodenectomy might improve postoperative glucose homeostasis because the velocity of gastric emptying is an important factor predicting the postprandial glucose level. This hypothesis explains the improvement in metabolic state even after proximal pancreatic resection for chronic pancreatitis. Further studies of patients who undergo pancreatic resection for the treatment of benign or borderline tumorous lesions of the pancreatic head are required to elucidate the mechanisms underlying the impact of pancreatoduodenectomy on glucose homeostasis [031].

Total pancreatectomy

Total pancreatectomy is performed for the multiple benign tumors requiring surgical intervention, refractory chronic pancreatitis and widely spreading tumor still having surgical implication. This procedure is also performed in order to rescue the patient with severe pancreatic fistula or abdominal hemorrhage after pancreatic resection. After pancreatic resection, recurrent tumor within remnant pancreas occasionally requires surgical resection, resulting in total pancreatectomy at the end. Unlike other pancreatic resection procedure, total pancreatectomy causes 100 percent of pancreatic diabetes. The lack of the pancreatic hormone leads to the extreme manifestation of the pancreatic diabetes [031].

Medical treatment

Despite the desire to avoid pancreatogenic diabetes after pancreatic resection, most cases require classical surgical resection, pancreatoduodenectomy, or distal pancreatectomy, for treatment of pancreatic tumors. When diabetes mellitus is mild, diet modification, exercise and/or pharmacological treatment are appropriate. Total pancreatectomy results in insulin dependent pancreatogenic diabetes and the long-term outcomes of diabetic control have been studied. Jethwa et al reported that the control of diabetes after total pancreatectomy is not necessarily associated with poor, relative to type 1 diabetes mellitus, glycemic control. In addition, the quality of life of patients after total pancreatectomy, performed to treat malignancy or chronic pancreatitis, is not always worse than previously considered. However, hypoglycemia-related mortality and complications, such as nephropathy, neuropathy and retinopathy, should be taken into consideration. Hypoglycemic attacks after exogenous insulin replacement are partly related to a deficiency in pancreatic enzymes. The keen observations of Linehan et al in 1988 from a series of total pancreatectomies revealed that the correct dose of pancreatic enzymes can produce optimal glycemic control and increase insulin demand, although these observations were not backed up by specific data. They proposed that rapid intestinal transit due to pancreatic insufficiency results in unpredictable glucose absorption and different levels of glucose uptake for every meal thus putting patients at risk of iatrogenic hypoglycemic attack. If this is true, then pancreatic enzyme supplementation is necessary not only to avoid exocrine insufficiency but also to achieve better glycemic control. In terms of parameters related to glycemic control, such as fasting glucose and HbA1c levels, the efficacy of pancreatic enzyme supplementation is controversial. However, one study demonstrated pancreatic supplementation to reduce the incidence of hypoglycemic attacks in patients with chronic pancreatitis and diabetes mellitus [031].

The usefulness of artificial endocrine pancreas in controlling blood glucose concentrations in hospitalized patients was recently demonstrated. This equipment continuously monitors blood glucose concentrations by withdrawing blood from a peripheral vein and administers insulin or glucose at rates determined to maintain the target glucose concentration. Artificial endocrine pancreas was shown to be safe and efficient in achieving tight perioperative blood glucose control without hypoglycemic episodes even immediately after total pancreatectomy. Together with insulin replacement therapy, PP administration might alleviate the difficulties associated with controlling glucose levels. PP administration reportedly upregulates hepatic sensitivity to insulin and therefore might improve the clinical outcome of glycemic control. However, the impact of glycemic control, in terms of preventing diabetes-related complications in the clinical setting, is not yet clear. Islet autotransplantation has been performed in certain institutes for the treatment of pancreatogenic diabetes mellitus following total pancreatectomy. Webb et al recently investigated the long-term outcomes of total pancreatectomy and simultaneous islet auto-transplantation in 46 patients mostly with chronic pancreatitis. Of these patients, 12 were insulin-independent for a median of 16.5

months. Employing the C-peptide assay this study also revealed that transplanted islets were functional in the long-term while the HbA1c level gradually increased after the operation. During follow-up, serum creatinine levels increased slightly, which was explained as an age-related increment in serum creatinine. They concluded that long-term insulin independence is not a usual outcome of islet auto-transplantation after total pancreatectomy. However, performance of this technique after total pancreatectomy achieves better glycemic control and can prevent diabetic complications. A limitation of this technique is that it can only be used to treat patients with benign diseases at qualified institutes. Microcapsuled islet transplantation might overcome the several problems entailed by the technique including immunosuppressant side effects if used and the possibility of spreading the malignant cells when auto-transplantation is performed in patients with pancreatic adenocarcinoma. However, the efficacy of this procedure needs further improvement. Another disadvantage of islet auto-transplantation seems to be associated morbidities such as portal thrombosis and splenic ischemia. Although total pancreatectomy itself holds these surgical complications, differentiating the cause of complication is still difficult in part due to lack of adequate amount of cases. Therefore, prevention of these complications derived from different causes and treatment strategies remain an obstacle [031].

The drugs which are typically used for the treatment of T3cDM are the same as for T2DM. In addition to insulin, therapeutic agents fall into three categories:

- insulin secretagogues that act on the sulfonylurea receptor complex or the incretin (GIP and GLP-1) receptors of the beta-cell
- agents that increase insulin sensitivity by their actions on liver, skeletal muscle or adipose tissue
- agents that principally affect absorption of glucose .

Sulfonylureas remain the most widely prescribed drugs for treating hyperglycemia. The meglitinide analog repaglinide and the D-phenylalanine derivative nateglinide also bind the sulfonylurea receptor and stimulate insulin secretion. The DPP-IV inhibitors and exenatide mimic incretin effects with the goal of raising endogenous insulin levels. Whereas metformin works primarily in the liver to decrease HGP and enhance insulin action, the peroxisome proliferator-activated receptor (PPAR) agonists rosiglitazone and pioglitazone appear to have their main effects on skeletal muscle and adipose tissue [030].

The choice of insulin versus non-insulin therapy for the initial treatment of T3cDM depends on the clinical presentation of the patient. For patients who are profoundly hyperglycemic (fasting glucose ≥ 10 mmol/l or 180 mg/dl, and A1c levels ≥ 8.5 %) and catabolic with glycosuria and weight loss, insulin treatment is preferred. It should be remembered that due to enhanced peripheral sensitivity to insulin, the dose of insulin required to achieve and maintain glycemic control in T3cDM may be significantly less than that seen in other insulin-dependent patients. Acutely ill patients who are hyperosmolar or ketotic require hospitalization for initial glycemic control, although this presentation is rare in T3cDM. More commonly, insulin therapy can be initiated on an outpatient basis, and usually starts with a bedtime dose of 10 U or 0.2 U/kg of an intermediate-acting insulin, or a bedtime or morning dose of a long-acting insulin, with progressive increases in insulin dose made every 3 days based on fasting and postprandial finger-stick blood glucose determinations. The goal is to reduce fasting glucose levels to the normal range of 3.9-7.2 mmol/L or 70–130 mg/dL and to reduce A1c levels to less than 7 percent. A combination of long-acting and intermediate-acting insulin administered morning and evening is frequently required. For the majority of T3cDM patients who are hyperglycemic (fasting blood glucose ≥ 7.0 mmol/l or 126 mg/dl), or whose 2-hour blood glucose after 75 g oral glucose is ≥ 11.1 mmol/l or 200 mg/dl, oral therapy can be initiated with periodic retesting of A1c level to determine the need to adjust dosing. Metformin is the preferred initial oral therapy in T2DM, due to its relatively low cost, low incidence of hypoglycemia, and absence of weight gain on therapy. In T3cDM, metformin is

the initial drug of choice for oral therapy due in part to its insulin-lowering effects on glucose metabolism, and also due to its specific anti-neoplastic actions on cellular mediators of replication and protein synthesis. Initiating therapy with metformin requires a dose titration to determine optimum therapy. Titration of metformin:

- Begin with low dose (500 mg) metformin taken once or twice a day (before breakfast and/or dinner) or 850 mg once a day (before breakfast)
- After 5–7 days, if gastrointestinal side effects have not occurred, advance dose to 850-1,000 mg twice a day
- If gastrointestinal side effects appear as dose is increased, drop back to previous dose and wait an additional 2-4 weeks before increasing dose again
- Maximum effective dose is 1,000 mg twice a day, although dose increase to 2,500 mg/day may have greater effectiveness if gastrointestinal side effects do not intervene
- Generic metformin is preferred due to cost considerations, but a longer-acting formulation available in some countries may allow once-a-day dosing. Metformin is contraindicated in patients with renal failure or when glomerular filtration rate falls to <30 mL/min

Agents from a different class of drug (such as a thiazolidinedione) can be combined with beneficial effects, although sulfonylureas, GLP-1 analogs, and DPP-IV inhibitors may be best avoided in T3cDM until clinical trials confirm their safety. Weight loss in obese subjects, daily exercise, a diet limited in carbohydrates, abstinence from alcohol and smoking cessation are critical elements which should be described and reinforced at every medical visit [030].

Isolation of human islets from partially pancreatectomized patients

Investigations into the pathogenesis of type 2 diabetes and islets of Langerhans malfunction have been hampered by the limited availability of type 2 diabetic islets from organ donors. It was now shared a protocol for isolating islets from human pancreatic tissue obtained from type 2 diabetic and non-diabetic patients who have undergone partial pancreatectomy due to different pancreatic diseases (benign or malignant pancreatic tumors, chronic pancreatitis, and common bile duct or duodenal tumors). All patients involved gave their consent to this study, which had also been approved by the local ethics committee. The surgical specimens were immediately delivered to the pathologist who selected soft and healthy appearing pancreatic tissue for islet isolation, retaining the damaged tissue for diagnostic purposes. It was found that to isolate more than 1,000 islets, one had to begin with at least 2 g of pancreatic tissue. Also essential to our protocol was to visibly distend the tissue when injecting the enzyme-containing media and subsequently mince it to aid digestion by increasing the surface area. To extend the applicability of our protocol to include the occasional case in which a large amount (>15g) of human pancreatic tissue is available, we used a Ricordi chamber (50 ml) to digest the tissue. During digestion, we manually shook the Ricordi chamber(3) at an intensity that varied by specimen according to its level of tissue fibrosis. A discontinuous Ficoll gradient was then used to separate the islets from acinar tissue. We noted that the tissue pellet should be small enough to be homogeneously resuspended in Ficoll medium with a density of 1.125 g/ml. After isolation, we cultured the islets under stress free conditions (no shaking or rotation) with 5 percent CO₂ at 37°C for at least 48 h in order to facilitate their functional recovery. Widespread application of this protocol and its future improvement could enable the timely harvesting of large quantities of human islets from diabetic and clinically matched non-diabetic subjects, greatly advancing type 2 diabetes research [033]

ENDOSCOPY

Endoscopic ultrasonography

Assess intraobserver agreement among endosonographers for endoscopic ultrasound (EUS) features of chronic pancreatitis (CP). Thirty EUS images from patients with suspected CP were shown twice in random order to five blinded endosonographers. The following accepted features of CP were assessed: hyperechoic foci, hyperechoic strands, lobularity, cysts, stones, main pancreatic duct dilatation, pancreatic duct irregularity, hyperechoic duct margins, visible side branches, and overall assessment for CP. The mean intraobserver (kappa) values were 0.82, 0.65, 0.71, 0.59, and 0.86 for the 5 endosonographers. The mean intraobserver [kappa] values for each feature were 0.66, 0.67, 0.70, not calculable, 0.96, 0.81, 0.77, 0.69, 0.51, and 0.73. The mean interobserver (kappa) values were 0.19, 0.07, 0.53, not calculable, 0.77, 0.77, 0.60, 0.34, 0.11, and 0.39, respectively. It was concluded that there was good intraobserver agreement in the interpretation of EUS features of CP. The intraobserver agreement seems better than the published interobserver agreement for EUS features of CP and better than the published intraobserver agreement for endoscopic retrograde cholangiopancreatography imaging for CP [034].

The objectives of one study were to compare endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) in the etiological diagnosis of patients initially diagnosed with idiopathic acute pancreatitis and to determine the clinical and analytical factors related to the end result of these techniques. Forty-nine patients, initially diagnosed with idiopathic acute pancreatitis, were evaluated prospectively with EUS and MRCP. Diagnoses were compared between the 2 procedures. The clinical-evolutionary characteristics of these patients with regard to the results obtained with these techniques were compared. In twenty-eight patients (57 %), EUS and/or MRCP diagnosed at least 1 possible cause of acute pancreatitis. The diagnostic yield of EUS was higher than that of MRCP (51 % vs 20 %). Cholelithiasis and biliary sludge (24 %) were the most frequent EUS diagnoses, and pancreas divisum (8 %) was the most frequent MRCP diagnosis. Only in 3 cases (6 %) did MRCP identify additional features in patients etiologically undiagnosed using EUS. The EUS yield was lower in patients who had a previous cholecystectomy (11 % vs 60 %). Thus, endoscopic ultrasonography and MRCP are useful techniques in the etiological diagnosis of acute pancreatitis of nonestablished cause. Endoscopic ultrasonography should be preferred for establishing a possible biliary etiology in patients who have not had a cholecystectomy [035].

Front-viewing endoscopic ultrasonography

A forward-viewing echoendoscope (FV-CLA) has been recently developed for performing interventional endoscopic ultrasound (EUS). The role of FV-CLA in performing standard EUS-guided fine-needle aspiration (FNA), Tru-cut biopsy (TCB), and celiac plexus neurolysis (CPN) is unknown. The aims were now to evaluate the feasibility of the FV-CLA for performing EUS-guided FNA/TCB and CPN. In the prospective study conducted over a 3-month period, 30 patients were evaluated with the FV-CLA. Procedures performed were FNA in 28 lesions, TCB in one, and CPN in five patients. EUS-guided FNA was undertaken at the following sites: mediastinum (n=3), liver (n=2), retroperitoneal mass (n=2), pancreas head/uncinate (n=9), pancreas body (n=6), pancreas tail (n=4), and perigastric lymph node (n=2). The median size of the lesions was 37x34 mm. A median of two passes was performed (range: 1-7). Final cytopathology diagnosed malignancies in 21 patients, with adenocarcinoma suspected for one. TCB of a mediastinal lymph node revealed lymphoma. FNA was benign in six patients. The sensitivity, specificity, positive predictive value, and

negative predictive value for a malignancy diagnosis was 96, 100, 100 and 86 percent respectively. CPN was successful in all five patients. It was easier to deploy the needle from the echoendoscope at all locations, including the duodenum, and irrespective of the site of the lesion. It was concluded that the initial evaluation and safety profile of the FV-CLA echoendoscope for performing standard FNA/TCB and CPN appear to be favorable. The narrow image does not preclude basic therapeutic maneuvers. A major advantage appears to be easy needle deployment at any site within reach of the echoendoscope [036].

Contrast-enhanced endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is superior to all other imaging modalities in detecting small pancreatic cancers. However, its ability to characterize hypoechoic pancreatic masses is limited: most carcinomas, neuroendocrine tumors, and inflammatory pseudotumors are simply depicted as hypoechoic masses. Contrast enhancement helps EUS to characterize such hypoechoic masses. Intravenous ultrasound (US) agents increase the signal from the blood and, thus, act as amplifiers and improve visualization of blood flow in small vessels using Doppler US. Contrast-enhanced Doppler EUS can differentiate small pancreatic carcinomas that cannot be detected by other imaging modalities. The development of second-generation US contrast agents and an EUS system with a broad-band transducer enabled the visualization of microvessels and the parenchymal perfusion in the pancreas. This contrast-enhanced harmonic EUS has shown that most pancreatic cancers exhibit hypovascular heterogeneous enhancement with irregular network-like microvessels. Moreover, it can diagnose pancreatic cancers with a high sensitivity (89-92 %) [037].

One study aimed to investigate the usefulness of contrast-enhanced endoscopic ultrasonography (EUS) with time-intensity curve (TIC) in differentiating pancreatic diseases. Patients who underwent contrast-enhanced EUS between 2007 and 2009 were analyzed retrospectively, including 48 with pancreatic ductal cancer (PC), 14 with autoimmune pancreatitis (AIP), 13 with mass-forming pancreatitis (MFP), and 16 with pancreatic endocrine tumor (PET). After intravenous injection of contrast agent, contrast imaging pattern, TIC-based quantitative evaluation, and diagnostic ability of EUS in combination with TIC to diagnose benignancy or malignancy were assessed. Hypovascular and heterogeneous pattern (42/48) in PC, isovascular and homogenous (21/27) in AIP and MFP, and hypervascular and rapid stained (16/16) in PET were observed. The echo intensity reduction rate from the peak at 1 minute was the greatest in PC followed by MFP, AIP, and PET. The diagnostic accuracies based on contrast imaging pattern (84 %) and TIC (88 %) were higher than those based on B-mode imaging (83 %) and dynamic computed tomography (81 %). In EUS in combination with TIC, sensitivity, specificity, and accuracy rose up to 96 percent, 93 percent, and 95 percent, respectively. Contrast-enhanced EUS with the dynamic quantitative analysis preparing TIC increased the diagnostic accuracy for pancreatic diseases [038].

Endoscopic ultrasound-guided fine needle aspiration

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is central to discerning the diagnosis of solid pancreatic tumors through tissue acquisition. Test performance is affected by a number of factors including location of mass within the pancreas, presence of onsite cytology technologist, and number of passes with the needle. The influence of tumor size has not been well studied. The objective of one study was to determine whether the size of mass affects the diagnostic accuracy for solid pancreatic lesions aspirated under EUS guidance. Data were collected retrospectively on all patients with solid pancreatic masses undergoing EUS-FNA from 2003 to 2010. The cytology samples were reported as positive, suspicious for malignancy, atypical, negative, or nondiagnostic. The gold standard for a cytological

diagnosis was histological confirmation or clinical follow-up of more than 6 months with repeat imaging. Patients were divided into five groups based upon lesion size as follows: less than 1 cm, 1-2 cm, 2-3 cm, 3-4 cm, and greater than 4 cm. Performance characteristics of EUS-FNA including sensitivity, specificity, and accuracy were compared for each group. Accuracy was defined as the ratio of the sum of true-positive and true-negative values divided by the number of lesions. It was identified 583 patients with solid pancreatic lesions in which EUS-FNA was performed and adequate cellularity was obtained (47 % men, mean age 65 ± 1 (SEM) years). Overall, 486 (83 %) of lesions were pancreatic adenocarcinoma, 18 (3 %) were neuroendocrine tumors, 12 (2 %) were lymphomas, and 67 (12 %) were benign lesions. The median size of the mass was 3 cm (range, 0.5-7 cm). A mean of 5 passes (range, 1-9 passes) was needed to obtain adequate samples from lesions. The overall yield of obtaining adequate samples for diagnosis was 85 percent. When stratified by size, the EUS-FNA sensitivity for lesions with size <1, 1-2, 2-3, 3-4, and >4 cm was 40, 76, 87, 93, and 92 %, respectively; EUS-FNA sensitivity strongly correlate with tumor size. Similarly, the accuracy of EUS-FNA increased as lesion size increased, ranging from 47 percent for tumors less than 1 cm to 88 percent for tumors greater than 4 cm. Location of tumor and number of needle passes did not significantly influence EUS-FNA performance characteristics. It was concluded that the sensitivity and diagnostic accuracy of EUS-FNA for solid pancreatic lesions is strongly correlated with tumor size. Sensitivity and accuracy decrease significantly for tumors that are smaller than 1 cm [039].

Endoscopic ultrasound (EUS) provides detailed, high-resolution images of the pancreas. However, whether a lesion is malignant or benign cannot be diagnosed solely from its imaging features on EUS. The introduction of EUS-guided fine needle aspiration (EUS-FNA) offers the possibility to obtain a cytological or histological diagnosis of pancreatic lesions with a high sensitivity and specificity. Although the clinical utility of EUS-FNA for pancreatic diseases is widely accepted, the indication for preoperative tissue diagnosis of pancreatic lesions suspected to be malignant is still controversial. This review highlights the diagnostic potential of EUS-FNA, as well as its current indications and contraindications, complications, and techniques [040].

To evaluate the diagnostic utility of endoscopic ultrasound guided fine needle aspiration cytology in the diagnosis of mediastinal and abdominal lesions endoscopic ultrasound guided aspiration cytology was carried out on a total of 155 cases during the study period. The lesions were categorized according to the site of needle biopsy. Clinical impression and provisional diagnoses were compared with the final cytological diagnoses and the percentage of inadequate/non diagnostic smears was calculated. Out of 155 cases, 18 cases (12 %) were reported as inadequate while a definite diagnosis was given in the remaining cases (89 %). The mean patient age was 49 ± 14 years. There were 105 (68 %) males and 50 (32 %) females. The most common site biopsied was mediastinal lymph nodes followed by pancreas. The most frequent diagnosis was adenocarcinoma mostly of pancreas followed by chronic granulomatous inflammation of mediastinal and abdominal lymph nodes. The average number of passes made was 3. The size of the lesions ranged from 0.6 cm to 25 cm with mean size of 3 cm as measured by endoscopic ultrasound probe [041].

Endoscopic Ultrasound (EUS) and the EUS guided fine-needle aspiration (EUS-FNA) increasingly plays an important role in the diagnostic evaluation of lesions or lymph nodes in the mediastinum and upper gastrointestinal tract of unknown origin. The objective of this study was to assess safety and accuracy of EUS-FNA in two secondary and tertiary health care providers. Prospectively, from 2003 to 2007, all patients underwent EUS with devices from Pentax with EUS-FNA. In all cases, cytology and extracted cells were histological examined by the same pathologists. In case of negative EUS results, patients were observed for at least 12 months after initial diagnosis later by reanalysis, CT-scan and follow-up clinical data to confirm the diagnosis. In total, 776 patients with EUS and 167 EUS-FNA (22 %) could be evaluated. Median age was 62 years, 68 percent of patients were male. Patients

underwent EUS-FNA in the mediastinum (n=54), pancreas (n=73), stomach (n=13), liver, adrenal glands and rectum (n=6). The complication rate of EUS-FNA was very low with only 0.6 percent, mainly consistent of one minor haemorrhage at the aspiration site. A clear histological diagnosis could not be achieved in 13 percent (21/167). Statistical analyses of all EUS-FNA revealed a sensitivity of 78 percent (95 % confidence interval 67 to 86) and a specificity of 99 percent (95 % confidence interval 92 to 100), with a positive and negative predictive value of 98 percent and of 78 percent, respectively. The overall accuracy was 87 percent (95 % confidence interval 80 to 92). It was concluded that EUS combined with FNA is a safe tool for first histological evaluation of unidentified lesions or lymph nodes in the mediastinum and upper gastrointestinal tract, indicative for gastrointestinal cancers [042].

Result delivery

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) is used for the diagnosis of pancreatic malignancy. However, there are limited data as to patient preferences regarding the delivery of cancer diagnoses. One study aimed to assess if patients had met the endosonographer before their EUS, their suspicion of having cancer, and whether they would like the cytology results given to them by their referring physician (with whom they had a previous relationship) or the endosonographer. This question was also asked with respect to the timing of receiving cytology results. A total of 131 patients with a suspected solid pancreatic mass undergoing EUS-FNA at two tertiary referral centers were prospectively enrolled and completed a preprocedure questionnaire. One hundred twenty patients (92 %) had not met the endosonographer before their EUS-FNA, and only 37 patients (28 %) thought they had a pancreatic malignancy. Of the 131 patients, 89 (68 %) stated that they wanted to hear results from the endosonographer and 100 patients (76 %) chose to hear results as soon as possible from the endosonographer. The data highlight the importance of the endosonographer's role in the delivery of cancer diagnoses and that patients value expediency of reporting results over long-term physician relationships [043].

Endoscopic ultrasonography-guided biliary drainage (choledochoduodenostomy)

Endoscopic ultrasonography (EUS)-guided choledochoduodenostomy (CDS) is as an alternative to percutaneous transhepatic biliary drainage (PTBD) in patients with biliary obstruction when endoscopic retrograde biliary drainage (ERBD) is unsuccessful. Over a 2-year period to 2008, 15 patients with unsuccessful ERBD underwent EUS-CDS. EUS-guided needle puncture was performed to access the bile duct from the duodenal bulb. After cholangiography, a guidewire was inserted through the needle and directed to the hepatic hilum. The punctured fistula was then dilated with a biliary dilator and a plastic stent was inserted. The technical success rate of EUS-CDS was 93 percent (14/15 patients); 1 patient underwent an EUS-guided rendezvous approach because the choledochoduodenal fistula could not be dilated. Decompression of the bile duct was achieved in all patients. Complications included cholangitis in 4 patients, self-limiting local peritonitis in 2 and distal stent migration in 1 patient. The median follow-up time was 125 days and the median duration of stent patency was 99 days. It was concluded that EUS-CDS may be effective for patients following unsuccessful ERBD and offers an attractive alternative to PTBD [044].

Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) has recently been reported as an alternative to percutaneous transhepatic biliary drainage (PTBD) in cases of biliary obstruction, when endoscopic biliary drainage (EBD) is unsuccessful. However, prospective studies of EUS-CDS have not yet been performed. We conducted a prospective study to evaluate the safety, feasibility, and efficacy of EUS-CDS in patients with malignant lower biliary tract obstruction. A prospective study to confirm the safety of EUS-CDS was carried out in 6 patients, followed by a trial to evaluate the feasibility and efficacy of EUS-CDS in 12 additional patients. It was placed a plastic stent from the duodenal bulb into the extrahepatic bile duct under EUS guidance using an oblique viewing echoendoscope, needle

knife, guidewire, and biliary dilators. The site of extrahepatic bile duct puncture was the common hepatic duct in 15 patients and the common bile duct in 3 patients. Mean diameter of the punctured extrahepatic bile ducts was 10 mm (range: 6-20 mm). Technical and functional success rates were 94 percent (17/18) and 100% (17/17), respectively. Median procedure time was 30 min (range: 10-52 min). Median duration to first oral intake after the procedure was 1 day (range: 1-3 days). Early complications were encountered in three (17 %) patients, including focal peritonitis in two patients and hemobilia in one patient. During the follow-up period (median: 163 days; range: 46-484 days), 12 stent occlusion events were observed in nine patients. Re-intervention with exchange of the occluded stent was successful in 8 of 12 (66 %) times. Severe early and late complications were not encountered in any patients in this study. Median duration of stent patency by Kaplan-Meier analysis was 272 days. It was concluded that EUS-CDS is safe, feasible, and effective as an alternative to PTBD and EBD in cases of malignant distal biliary tract obstruction. Prospective randomized studies are needed to compare the safety and efficacy of various kinds of endoscopic devices used in EUS-CDS and to compare EUS-CDS with PTBD or EBD [045].

ERCP

As the population ages, endoscopic retrograde cholangiopancreatography (ERCP) is being used increasingly as a diagnostic and therapeutic tool for elderly patients with pancreatobiliary disease. The aim of this study was to assess the outcomes, safety and complications associated with ERCP performed in the elderly patients. It was retrospectively reviewed the medical record of 596 patients who were 50 years of age or older and underwent ERCP from 2005 to 2010. The patients were classified into two groups according to the age: non-elderly, 50-74 years old and elderly, ≥ 75 years old. Comparisons were made between two groups. Five hundred and ninety-six patients (132 elderly and 464 non-elderly patients) were enrolled. The success rate of ERCP was 89 percent in the elderly and 92 percent in the non-elderly. The major complications were occurred in 11 patients of the elderly and 16 of the non-elderly, and the complication rate was significantly higher in the elderly compared to the non-elderly (8 % vs 3 %). Pancreatitis occurred in 2 elderly patients and 10 non-elderly patients (2 % vs 2 %). There was a higher rate of bleeding in the elderly patients (5 % vs 1 %). It was concluded that ERCP is effective and safe even in elderly patients. Outcomes of diagnostic and therapeutic ERCP in the elderly patients were similar to those in non-elderly patients. Elderly patients undergoing ERCP carried similar risk of pancreatitis but a higher risk of bleeding and perforation compared to non-elderly patients [046].

Transgastrostomy ERCP in patients with Roux-en-Y anatomy

Roux-en-Y gastric bypass (RYGB) surgery is one of the most commonly performed bariatric surgeries in the United States. Patients with prior RYGB are not amenable to conventional endoscopic retrograde cholangiopancreatography (ERCP). Surgical gastrostomy (SG) tube placement enables transgastrostomy ERCP (TG-ERCP). Eleven patients with RYGB anatomy received open Stamm gastrostomy after which the tract was then allowed to mature for an average of 45 days before therapeutic TG-ERCP. The success rate and procedure-related complications of both gastrostomy and ERCP were assessed. TG-ERCP was performed on eleven patients (median age 52 years, range 37-61 years) with prior RYGB and pancreatobiliary diseases. Indications for ERCP in these patients included suspected gallstone pancreatitis (n=4), ampullary/biliary strictures (n=5), pancreas divisum (n=1), and common bile duct clipping as a result of RYGB surgery (n=1). Two individuals developed post surgical complications with stomal-related infections. TG-ERCP with therapeutic

intervention was successfully performed in all patients. Intervention included stone extractions (n=11), biliary stricture dilation (n=11), biliary sphincterotomy (n=11), biliary (n=3) and pancreatic (n=1) stent placement, ampullary biopsies (n=3), choledochoscopy (n=1), and pseudocyst drainage (n=1). Complications included post-ERCP pancreatitis (n=2), post-sphincterotomy bleeding (n=1), gastrostomy site bleed (n=1), and gastric perforation (n=1). The total number of ERCP sessions for the eleven patients was 15 (1 or 2 per patient). Median follow-up was 42 days (range 7-123 days). It was concluded that surgical open gastrostomy followed by TG-ERCP enables therapeutic intervention but is associated with significant complications [047].

Endoscopic pancreatic stenting

A 79-year-old man was admitted on the suspicion of acute pancreatitis. Computed tomography showed acute fluid collection but not typical acute pancreatitis; it formed pseudocysts gradually around the pancreas. Endoscopic retrograde pancreatography (ERP) revealed pancreatic disruption and leakage. Endoscopic nasopancreatic drainage (ENPD) and endoscopic pancreatic stenting (EPS) resulted in collapse of pseudocysts, improvement of symptoms and laboratory data, and a mass in the pancreatic body became distinct. The specimens obtained with endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) showed pancreatic cancer. In conclusion, ENPD and EPS are effective for pancreatic leakage with disruption of the pancreatic duct, and we should take into consideration the possibility of pancreatic cancer when we see patients with pancreatic disruption [048].

Covered self-expandable metal stent

It was reported a retrospective analysis of patients with malignant biliary obstruction in whom a newly released fully silicon-covered, WallFlex, self-expandable metal stent (CSEMS) was placed for biliary decompression. Between 2009 and 2010 all patients with obstructive jaundice secondary to pancreatic cancer underwent placement of a CSEMS, regardless of resectability. A CSEMS was placed across the malignant stricture. These patients were then staged for their cancer by computed tomography, magnetic resonance imaging, and/or endoscopic ultrasound-guided fine-needle aspiration. Patient found to have resectable cancer were offered a pancreaticoduodenectomy. It was identified 88 patients with pancreatic cancer who received a CSEMS. Forty patients were deemed resectable and underwent surgery. Pancreaticoduodenectomy was performed in 34 of 40 patients. The CSEMS was easily removed at the time of surgical resection without any complications. The 44 unresected patients with covered SEMS were followed for a mean of 4.2 months (range, 1 to 13). The patency rate for stents was 97 percent at 12 months. Immediate procedural complications included post-endoscopic retrograde cholangiopancreatography pancreatitis (n=9) and duodenal perforation (n=2). Four patients (5 %) had migration and 3 (3 %) had stent occlusion. There were no cases of cholecystitis during the follow-up. The patients who presented with stent migration or occlusion underwent stent revision. It was concluded that placement of the newly available CSEMS can be used to effectively and safely treat biliary obstructions from pancreatic carcinoma. We recommend that the CSEMS be used as an initial intervention to relieve malignant biliary obstruction, even in patients whose surgical resectability status is uncertain [049].

Double stent system for palliative treatment

The purpose of this study is to investigate the efficacy and safety of a novel double stent in patients with malignant extrahepatic biliary obstruction. This prospective pilot study enrolled

45 consecutive patients with malignant extrahepatic biliary obstructions from January 2008 to December 2009. All patients were treated with a novel double stent system (covered stent in uncovered stent). The double stents were successfully placed in all patients. Bilirubin levels decreased significantly after stent placement. Median patient survival and stent patency times were 149 days (95 % confidence interval 126 to 172 days) and 439 days (95 % confidence interval 123 to 755 days), respectively. Cumulative stent patency rates at 3, 6, 9, and 12 months were 91, 89, 82, and 82 percent, respectively. Five patients (11 %) presented with stent occlusion due to tumor overgrowth (n=3) or sludge incrustation (n=2) and required repeat intervention. Tumor ingrowth, acute cholecystitis, pancreatitis, or stent migration was not observed in any of these patients. Thus, preliminary results indicate that percutaneous treatment of malignant extrahepatic biliary obstructions using a novel double stent is feasible, safe, and effective in achieving internal biliary drainage [050].

Endoscopic papillary large balloon dilatation

Endoscopic papillary large balloon dilatation (EPLBD) after endoscopic sphincterotomy (EST) has recently become widely used for common bile duct (CBD) stone removal, but many clinicians remain concerned about post-procedural pancreatitis with increasing the balloon size to over 15 mm. A retrospective review was undertaken of the endoscopic database of 101 patients with CBD stones who underwent EPLBD using a larger balloon size of over 15 mm (15-20 mm). Clinical parameters, endoscopic data, and outcomes were analyzed. The mean age of the subjects was 69 years. All patients had a dilated CBD of over 11 mm (mean = 23 mm). The mean size of balloon used in EPLBD was 17 ± 2 mm (range 15-20 mm). Mechanical lithotripsy was required in seven patients (7 %). The rate of complete stone removal in the first session was 92 percent. Post-procedural pancreatitis developed in five cases (5.4 %), but none were graded as severe. The smaller dilatation of the CBD, longer cannulation time, and longer time for stone removal were associated with post-procedural pancreatitis, but larger size of balloon did not affect the development of post-EPLBD pancreatitis. It was concluded that EPLBD with a large balloon of over 15 mm with EST is an effective and safe procedure with a very low probability of severe post-procedural pancreatitis. Post-EPLBD pancreatitis was not associated with larger balloon size, but was associated with longer procedure time and smaller dilatation of the CBD [051].

Prophylactic stents after ERCP

Prophylactic pancreatic duct (PD) stent placement has been shown to reduce the incidence of post-ERCP pancreatitis (PEP) especially in high-risk patients. However, there is no consensus on the best type of PD stent. The purpose of one study was to evaluate the differences in the outcomes between long (>3 cm) pigtail and short (≤ 3 cm) flanged 4 Fr Freeman Pancreatic Flexi-Stents in preventing PEP. It was retrospectively reviewed all ERCP procedures performed between 2006 and 2007 by one of two experienced endoscopists (>5 years of experience) with the assistance of a trainee. Patient data was collected for indications, risk factors for PEP, type and reason for PD stent, complications, and any mortality. The PD stent was removed endoscopically if it was still in place on abdominal X-ray done 2 weeks post-ERCP. Out of a total of 753 ERCP procedures, 179 (24 %) required either long or short prophylactic PD stents. The incidence of PEP was 4 percent versus 14 percent for long and short stent groups, respectively, which was a significant difference. Spontaneous stent dislodgement rate was 95 percent versus 82 percent for long and short stent groups, respectively, which also was a difference. There was no difference in non-pancreatic complications between the two stent groups. There was no procedure-related mortality. It was concluded that long (>3 cm) pigtail PD stent due to their specific design

showed better outcomes as compared to short (<3 cm) flanged PD stent in preventing PEP and spontaneous stent dislodgement rates [052].

Sphincterotomy for stent placement

Endoscopic retrograde cholangiopancreatography with biliary self-expanding metal stent placement is the preferred method of providing biliary drainage for pancreaticobiliary malignancies. Some endoscopists routinely perform biliary sphincterotomy to facilitate biliary stent placement and potentially minimize pancreatitis with transpapillary self-expanding metal stent placement. The hypothesis was now that biliary sphincterotomy has no effect on the success rate of transpapillary self-expanding metal stent placement and increases procedure-related complications. In a retrospective analysis, outcomes of two groups were compared: (1) self-expanding metal stent placement without biliary sphincterotomy, (2) self-expanding metal stent placement with biliary sphincterotomy during the same procedure. Complications and stent patency rates were evaluated. There were 104 subjects included in the study. Post-sphincterotomy bleeding was associated with biliary sphincterotomy performed immediately prior to self-expanding metal stent placement. Importantly, self-expanding metal stent placement without biliary sphincterotomy was always technically successful and self-expanding metal stent placement without biliary sphincterotomy was not associated with pancreatitis. Patients who undergo biliary sphincterotomy during transpapillary self-expanding metal stent placement experience more immediate complications than those who do not. Biliary sphincterotomy was not associated with longer stent patency. Self-expanding metal stent placement without a biliary sphincterotomy was not associated with pancreatitis regardless of the type of self-expanding metal stent used (covered or uncovered). Of the patients without a biliary sphincterotomy, 100 percent had successful stent placement, further arguing against its use in this setting [053].

Endoscopy in the elderly

Pancreatobiliary disease is increased in elderly patients. Because of significant comorbidities, these patients may be at greater risk of developing complications related to endoscopic retrograde cholangiopancreatography (ERCP). The purpose of one study was to compare the indications, interventions, and complications of ERCP of octogenarians with nonoctogenarians. A retrospective review of patient records from a single tertiary care hospital was performed. Adult patients undergoing ERCP were divided into two groups according to age. Group 1 patients were of age < 80 years (n=391), and group 2 patients were > 80 years of age (n=102). Indications, therapeutic interventions, use of conscious sedation, duration of procedure and complications were retrieved from the patient records. Main outcome measurements included: indications, therapeutic interventions, use of conscious sedation, duration of procedure and complications. There was an increase in sphincterotomy rates (74 vs 63 %) and stent insertions (48 vs 29 %) in the octogenarian group. In group 1 there were 19 cases (5 %) of post ERCP pancreatitis who spent 251 hospital days (including 59 ICU days) compared with one case (1 %) in group 2 who required ten hospital days and 0 ICU days. Procedure time for octogenarians was somewhat greater than nonoctogenarians (33 vs 30 min). Octogenarians required less conscious sedation than nonoctogenarians (midazolam 4.1 vs 5.9 mg; and fentanyl 46 vs 80 microg). It was concluded that in octogenarians, ERCP is efficacious and safe. It is associated with a lower rate of hospitalization for pancreatitis. ERCP in octogenarians takes longer, is associated with increased interventions (stent insertion and sphincterotomy) and requires less sedation [054].

Endoscopic elastography

Sonoelastography is based on the knowledge that some diseases, such as cancer, lead to a change in tissue hardness. Elastography examines the elastic properties of tissues by applying a slight compression to the tissue and comparing the images obtained before and after this compression. Endoscopic ultrasonography (EUS) is today the best technique to diagnose a small pancreatic mass and to determine the histology of such lesions. However, the accuracy of EUS-FNA is around 85-90%. In this study, elastography was used to differentiate benign from malignant pancreatic masses [055].

Anaesthesiology for ERCP

While some gastroenterologists provide their own sedation for endoscopic retrograde cholangiopancreatography (ERCP), others utilize anesthesiologists. There is limited information comparing cannulation success and complication rates between these two approaches. Theoretically, anesthesiologist-directed sedation (ADS) may lead to an improved deep cannulation rate by virtue of using deeper and more constant levels of sedation and by removing the minute-by-minute medication management and physiologic monitoring responsibilities from the endoscopy team. To compare ERCP deep cannulation success and complications between gastroenterologist-directed sedation (GDS) and ADS all ERCPs completed by senior advanced endoscopists at a tertiary referral center over a 2-year period were reviewed. During the first year, all ERCP sedation was performed with GDS utilizing a narcotic and a benzodiazepine. Due to a change in division policy and practice, during the second year, all ERCP sedation was provided by ADS. Patients with prior papillary interventions were excluded. Demographics, procedure indications, deep cannulation success, sedation provider, and procedural complications were recorded. A total of 367 patients were studied: 178 (49 %) GDS and 189 (52 %) ADS. There was no difference in the groups with respect to race, age, and gender. Four patients (2.3 %) in the GDS group could not be sedated. There were two deaths, one in each group; one death was due to cholangitis/sepsis and the other was due to post-ERCP pancreatitis. The overall cannulation success rates were similar between the two groups (94 % vs 95 %). Thus, deep ductal cannulation rates between GDS and ADS are similar [056].

Radiation risks in endoscopy

Fluoroscopy during endoscopic retrograde cholangiopancreatography (ERCP) has a logarithmic relationship with radiation exposure, and carries a known risk of radiation exposure to patients and staff. Factors associated with prolonged fluoroscopy duration have not been well delineated. To determine the specific patient, physician and procedural factors that affect fluoroscopy duration. A retrospective analysis of 1071 ERCPs performed at two tertiary care referral hospitals over an 18-month period was conducted. Patient, physician and procedural variables were recorded at the time of the procedure. The mean duration of 969 fluoroscopy procedures was 4.7 min (95 % confidence interval 4.38 to 4.93). Multivariable analysis showed that the specific patient factors associated with prolonged fluoroscopy duration included age and diagnosis. The endoscopist was found to play an important role in the duration of fluoroscopy (i.e. all endoscopists studied had a mean fluoroscopy duration significantly different from the reference endoscopist). In addition, the following procedural variables were found to be significant: number of procedures, basket use, biopsies, papillotomy and use of a tritome. Mean fluoroscopy duration (in minutes) were as follows: common bile duct stones (n=443) 5.1, benign biliary strictures (n=135) 3.9; malignant biliary strictures (n=124) 5.8; chronic pancreatitis (n=49) 4.5; bile leak (n=26) 3.7; and ampullary mass (n=11) 3.9. When no pathology was found (n=195), the mean

fluoroscopy time was 3.6 min (95 % confidence interval 3.1 to 4.1). Comparison using t tests determined that the only two diagnoses for which fluoroscopy duration was significantly different from the reference diagnosis of “no pathology found” were common bile duct stones and malignant strictures. It was concluded that factors that significantly affected fluoroscopy duration included age, diagnosis, endoscopist, and the number and nature of procedures performed. Elderly patients with biliary stones or a malignant stricture were likely to require the longest duration of fluoroscopy. These identified variables may help endoscopists predict which procedures are associated with prolonged fluoroscopy duration so that appropriate precautions can be undertaken [057].

OTHER GENERAL DIAGNOSTICS

Acute pancreatitis is one of the more commonly encountered aetiologies in the emergency setting and its incidence is rising. Presentations range from a mild-self limiting condition which usually responds to conservative management to one with significant morbidity and mortality in its most severe forms. While clinical criteria are necessary to make the initial diagnosis, contrast-enhanced CT is the mainstay of imaging and has a vital role in assessing the extent and evolution of the disease and its associated complications. The purpose of one article was to summarise the natural course of acute severe pancreatitis, clarify confusing nomenclature, demonstrate the morphological stages in conjunction with radiological scoring systems and illustrate the complications [058].

Enzyme testing

The reasons for increasing incidence of acute pancreatitis (AP) are not completely understood. It was hypothesized that the rate of serum pancreatic enzyme testing is increasing, and it correlates with AP diagnosis. It was retrieved electronic patient data for all emergency department visits at two university hospitals from 1996 to 2005 (n=422,745 + 202,171). It was evaluated the trends for serum pancreatic enzyme testing (amylase, lipase, or both) and correlated this with the proportion of visits resulting in an inpatient discharge diagnosis of AP. Serum enzyme testing increased significantly from 5 percent (95 % confidence interval 4 to 5) in 1996 to 10 percent (95 % confidence interval 9 to 10) in 2005. On multivariate modeling, the rates for serum pancreatic enzyme testing were higher among females (vs males) and increased with age. The proportion of emergency department visits resulting in an inpatient discharge diagnosis of AP increased significantly during the study period and correlated highly with the rate of enzyme testing. It was concluded that the rate of serum pancreatic enzyme testing is increasing [059].

CT

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 percent, respectively; mean variability in dual-energy iodine-mapping results was 24 %). The study thus 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 [060].

CT imaging of the pancreas during the intravenous (i.v.) contrast administration of iodinated, nonionic contrast material is an essential, indispensable technique for the diagnosis and evaluation of pancreatic inflammatory and neoplastic conditions. Data regarding timing, extent and pattern of pancreatic enhancement are used to develop protocols that increase the accuracy of CT imaging in detecting pancreatic pathology and in evaluating peripancreatic vascular structures. A clinical investigation study documented significant variations in the enhancement values of the normal pancreas in 20 patients who underwent perfusion CT imaging and in 10 patients who were scanned using a dual-energy protocol. There were the expected patient-to-patient differences in the enhancement values (intervariability) and additionally individual regional pancreatic variations between the head, body and tail of the pancreas in the degree of enhancement (intraindividuality). Regional intraindividuality showed maximum enhancement difference values ranging from 3 to 21 Hounsfield Units (HU) in the perfusion group and from 2 to 17 HU in the dual-energy CT group, without significant differences between these groups compared to the variability detected with simple HU density measurements. The authors concluded that given these normal variations in pancreatic tissue contrast enhancement, the use of cut-off values to characterize pancreatic pathology is unreliable and should not be used in clinical practice. These basic density and enhancement differences are common and large, often affecting the entire gland but sometimes only parts of the pancreatic gland. They are attributed to a variety of factors including age, BMI, cardiac status, atherosclerosis, fatty infiltration (spotty, focal or diffuse), volume and concentration of iodinated material injected, rate of i.v. perfusion and timing of image acquisition. While some of these factors can be controlled and standardized, many others cannot be changed or minimized, leading to wide variations in the enhancement values of the pancreas in different individuals. Focal fatty infiltration in the head of the pancreas, which is common can decrease even further the basic density and the expected enhancement values of the gland. The wide range of anticipated patient-to-patient basic and enhancing variability is consistent with these figures. Furthermore, when it was calculated the enhancing HU value of the head of the pancreas as a percentile of the enhancing value of the aorta at 80 s (the pancreatic enhancement coefficient), we obtained an average of 62 percent enhancement but with a wide range of 37-80 percent. This implies that in addition to systemic factors (BMI, age, cardiac status) other intrinsic local factors play a role in the degree and extent of pancreatic enhancement. The timing of the acquisition of imaging and age is important regarding the normal enhancing pattern and the peak enhancement time of the normal pancreas on multiphase MDCT examination. It has been shown that both the rate and volume of contrast material administered affect the degree of parenchyma enhancement. Regional differences of enhancement in the same individual between the head, body and tail of pancreas are not as well documented in the literature. Radiologists experienced in pancreatic CT imaging are familiar with slight enhancement variations throughout the pancreas, which are more difficult to explain. They may be caused by anatomic variations in the vascular supply of the pancreas, atherosclerosis with stenosis of the celiac trunk and/or superior mesenteric artery, or errors in collecting data such as size of the region of interest cursor, location of the cursor or volume average etc. Unforeseen differences in the enhancing values of the normal pancreas among various individuals and regional differences within the same gland should be expected and should have no significant impact on radiologic diagnosis. Cut-off enhancing values are not used in clinical practice in depicting inflammatory conditions. Also, visibly detectable areas of decreased or

increased enhancement compared to the surrounding gland (usually over 25-30 HU) are useful diagnostic indicators of the presence of pancreatic pathology. As such, they will continue to be used in clinical practice. Initial CT studies in patients with acute pancreatitis have associated lack of enhancement or only mild enhancement (<30 HU) of the pancreatic parenchyma, with the development of pancreatic necrosis. Since then, with the introduction of MDCT, improved and rapid i.v. perfusion rates and accumulated experience, it has been established that some patients with obvious low enhancing values will not develop pancreatic necrosis. Low HU values often detected within the first 24 h of onset are the result of decreased contrast perfusion secondary to pancreatic ischemia, which may be transitory or may progress to necrosis and severe edema and inflammation. It is now known and accepted that necrosis develops early, usually within 48-72 h after the clinical onset, when the normal texture of the pancreatic parenchyma liquefies and is replaced by lower attenuated homogeneous or slightly heterogeneous areas of necrotic tissue with density values as low as 10-30 HU. Thus, a low enhancing pancreatic parenchyma with preservation of the texture of the gland is suspicious but not diagnostic of pancreatic necrosis. These patients need follow-up CT examinations for confirmation. Similarly, the detection of a focal area of high or low attenuation compared with the surrounding pancreatic parenchyma is the hallmark of a pancreatic tumor until proven otherwise. It is acknowledged that associated morphologic changes, e.g. dilated pancreatic duct, pancreatic contour deformity arterial encasement, venous obstruction, common duct obstruction, metastases, gland atrophy, lymphadenopathy, etc. will confirm the diagnosis, but these abnormalities are not always present. The isolated discovery of a focal area of decreased attenuation independent of its enhancing values is seen with small pancreatic tumors and has a high positive predictive value, hence these patients should be further investigated with endoscopic sonography, MR imaging, endoscopic retrograde cholangio-pancreatography and endoscopic or percutaneous biopsies. Despite the normal regional variations of pancreatic enhancement, these findings cannot be ignored even when they may be secondary to fibrotic tissue seen in chronic pancreatitis or to slight differences in the normal enhancing pattern of the pancreas [061].

To assess the interfractional positional variation of the pancreas using four-dimensional computed tomography (4D-CT) and to determine the suitable phase of respiration for dose delivery methods to account for pancreatic tumor motion. Fifteen patients with pancreatic cancer were enrolled in this study. For each patient, 4D-CT scans were performed at CT simulation and three times during the course of treatment. Regions of interest were set to the intrapancreatic bile ducts as a surrogate for pancreatic position. The centroids of the regions of interest were calculated at end-inhalation and end-exhalation of the respiration phase. The ranges of respiratory motion and interfractional positional variation were evaluated in the left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions. The medians of respiratory motion were 1.1 mm (range, 0.0-9.8 mm), 1.5 mm (range, 0.0-7.0 mm), and 5.0 mm (range, 0.0-12.5 mm) in the LR, AP, and SI directions, respectively. The means \pm SDs of the interfractional positional variation at end-inhalation were 0.9 ± 5.1 mm (range, -9.2 to 15.6 mm), -1.9 ± 3.9 mm (range, -12.8 to 6.4 mm), and -1.3 ± 6.9 mm (range, -15.0 to 13.7 mm) and those at end-exhalation were 0.0 ± 3.1 mm (range, -7.0 to 5.3 mm), -1.2 ± 3.9 mm (range, -11.2 to 6.7 mm), and 0.1 ± 3.2 mm (range, -9.9 to 5.1 mm) in the LR, AP, and SI directions, respectively. The SDs of the interfractional positional variation in the LR and SI directions were significantly larger at end-inhalation than at end-exhalation. Thus, the ranges of respiratory motion during the course of treatment and the interfractional positional variation were not negligible. The interfractional positional reproducibility was higher at end-exhalation than at end-inhalation under free breathing [062].

To prospectively compare 320-detector volumetric and 64-detector helical computed tomographic (CT) images of the pancreas for depiction of anatomic structures, image noise, and radiation exposure a total of 154 patients (85 men, 69 women; age range, 26-85 years; mean age, 67 years) who underwent biphasic (arterial and pancreatic phase) contrast material-enhanced CT performed with a 320-detector scanner were randomized into two

groups: the 320-detector group and the 64-detector group. Biphasic transaxial multiplanar reformatted images and volume-rendered CT angiograms were obtained. CT numbers in the abdominal aorta, pancreas, and abdominal wall fat tissue; signal-to-noise ratio (SNR); and dose-length product (DLP) were compared. In addition, image quality and focal lesion depiction (n=35) were qualitatively determined in the two groups. No significant difference in CT numbers of the abdominal aorta and pancreas was noted between the two groups. Mean DLP was 43 percent lower in the 320-detector group (675 mGy·cm) than in the 64-detector group (1188 mGy·cm). SNR of the abdominal aorta, pancreas, and abdominal wall fat on biphasic images was significantly lower in the 320-detector group than in the 64-detector group. Image quality was acceptable in both groups and was slightly better in the 64-detector group for pancreatic phase axial images and arterial phase multiplanar reformatted images. No significant difference was found in the depiction of pancreatic parenchyma, main pancreatic duct, focal pancreatic lesions, splanchnic arteries, or most of the small splanchnic arterial branches. It was concluded that a 320-detector CT scan facilitates fast volumetric contrast-enhanced CT of the entire pancreas with acceptable image quality, even though SNR was significantly lower at 320-detector volumetric scanning [063].

Magnetic resonance imaging

To determine which of the quantitative parameters obtained from intravoxel incoherent motion diffusion weighted imaging (DWI) is the most significant for the differentiation between pancreatic carcinoma and mass-forming chronic pancreatitis 29 patients with pancreatic masses were included, 9 proved to have a mass-forming pancreatitis and 20 had a pancreatic carcinoma. The patients were studied using intravoxel incoherent motion DWI with 11 b-values and the apparent diffusion coefficient (ADC), the true diffusion constant (D) and the perfusion fraction (f) were calculated. The diagnostic strength of the parameters was evaluated using receiver operating characteristic analysis. The ADC in chronic pancreatitis was higher than in pancreatic carcinoma with significant differences at b = 50, 75, 100, 150, 200, 300 s/mm. No significant differences were found at b = 25, 400, 600, and 800 s/mm. The perfusion fraction was significantly higher in pancreatitis compared with pancreatic carcinoma. There was no significant difference between groups for D for chronic pancreatitis and for pancreatic carcinoma. It was concluded that there were significant differences in ADC50-300 between chronic pancreatitis and pancreatic carcinoma. Because D is not significantly different between groups, differences in ADC can be attributed mainly to differences in perfusion. The perfusion fraction f proved to be the superior DWI-derived parameter for differentiation of mass-forming pancreatitis and pancreatic carcinoma [064].

CLASSIFICATION OF ACUTE PANCREATITIS

Since the original Ranson criteria were published more than 30 years ago, few topics have engendered as much sustained interest as the prediction of outcome in acute pancreatitis. The two most common approaches to determining prognosis in acute pancreatitis are use of a clinical scoring system and measurement of specific laboratory tests. These prognostic markers should not be confused with the actual measures of severity that are used to classify the degree of illness a patient has. Measures of severity in acute pancreatitis were defined in the Atlanta classification system. These include either local complications (e.g. necrosis and acute collection of fluid) or persistent organ failure (e.g. shock, respiratory failure or renal insufficiency). When evaluating prognosis in acute pancreatitis, it is also important to consider the outcome that one is trying to predict and when such a prediction should be made. Most studies that evaluate prediction methods in acute pancreatitis have focused on death as the outcome of interest because it is a well-defined, clinically significant outcome. With respect to the timing of prediction, it is now clear that the first 24 hours after admission

to hospital are critical. To be of the greatest value to clinicians, predictions of outcome should be accurately and reliably applied as early as possible, preferably during the first 24 hours of admission to hospital. A prediction tool should also have a high level of sensitivity; underestimating the severity of pancreatitis can have life-threatening consequences. Although complex scoring systems such as the APACHE II are well suited to research purposes, a more simplified approach such as the BISAP is more likely to be helpful in routine clinical practice. In addition, serial measurement of blood urea nitrogen levels can be useful not only to rapidly identify patients at increased risk of death, but also to potentially help guide initial fluid resuscitation efforts [065].

Approximately 80 percent of patients with acute pancreatitis recover by 7 days while the other 20 percent have a more serious form described as severe acute pancreatitis (SAP). Among the group who do not resolve within 7 days, overall mortality is approximately 4 percent. The development of necrosis increases mortality risk to approximately 10 percent, with subsequent infection of necrotic pancreatic tissue increasing this risk further to about 25 percent [066].

Reporting of prognostic markers

The objective of one study was to assess the reporting of studies on new prognostic markers of outcome in acute pancreatitis. It was used MEDLINE searches complemented with perusal of review articles' references to identify eligible English-language studies. It was included studies evaluating nonroutine markers for acute pancreatitis. Eligible outcomes included Atlanta criteria, Japanese criteria for severity, multiple/single organ failure, complications, interventional treatment, hospitalization length, and death. It was generated a 47-item checklist on Acute Pancreatitis Prognosis by adapting a previously constructed reporting guidance instrument for prognostic tumor markers (REMARK [Reporting Recommendations for Tumor Marker Prognostic Studies]). The checklist addresses the reporting of essential information in prognostic studies. The 184 identified eligible studies reported on 196 different prognostic markers. One hundred forty-four studies (78 %) found at least 1 prognostic marker to be nominally statistically significant. Significant improvements over time were seen in the reporting for 17 items, but major deficiencies were noted even in 2004-2009 studies. Particularly, 12 items were reported in less than 10 percent of studies overall and even within the most recent studies. Despite some improvements over time, the reporting of important aspects of prognostic studies in acute pancreatitis remains suboptimal. The proposed REMARK-based checklist may help improve the quality and reporting of research in this field [067].

Acute Physiology and Chronic Health Examination (APACHE) II

The most widely used index for early risk stratification is the Acute Physiology and Chronic Health Examination (APACHE) II. Although more recent iterations of this scoring system have been developed, the advantages of the APACHE II are its familiarity, objective nature, and ability to be calculated at any time during a patient's stay in hospital. This scoring system has been widely validated for predicting death in acute pancreatitis. Most practice guidelines recommend a cut-off score of more than eight points at admission for prediction of severe disease, although several prospective observational studies have shown that specificity can be increased by raising the threshold to 10 points or more at admission (specificity 66 % to 81 %). Use of the APACHE II in clinical practice has several important limitations, such as the requirement for multiple parameters and the need for an online calculator (versions of which are widely available on the Internet). As a result, several additional scoring systems have been developed for bedside application [065].

Glasgow score

The modified Glasgow score was developed in the mid-1980s. This scoring system, which incorporates seven routine laboratory tests, as well as the patient's age, has been widely validated for the prediction of outcome in acute pancreatitis. Although simpler to use than the original Ranson criteria, the modified Glasgow score was similarly designed to be calculated 48 hours after admission to hospital [065].

Bedside Index of Severity in Acute Pancreatitis (BISAP)

A more recent scoring system developed for use during the first 24 hours of admission to hospital is the Bedside Index of Severity in Acute Pancreatitis (BISAP). This score was derived using data from a population of 17 992 patients and validated on a population of 18 256 patients in the United States. This five-factor scoring system (blood urea nitrogen > 8.9 mmol/L, impaired mental status, systemic inflammatory response syndrome, age > 60 years, and pleural effusion) was shown to have similar accuracy to the APACHE II for predicting death in the initial retrospective study and in several subsequent prospective cohort studies. The BISAP is a simplified scoring system that can be easily applied in the earliest phases of acute pancreatitis to help identify which patients have an increased risk of death [065].

SIRS

There has been interest in determining to what extent the development of systemic inflammatory response syndrome alone can be used to determine prognosis in acute pancreatitis. This four-factor syndrome, diagnosed on the basis of vital signs and the leukocyte count, first emerged from the literature on sepsis. Although the presence of the syndrome during the first 24 hours of admission to hospital has high sensitivities for predicting organ failure (85 %) and death (100 %), it lacks specificity for severe disease (41 %). Specificity is increased with the duration of the syndrome, such that persistent systemic inflammatory response syndrome (i.e. longer than 48 hours) has been linked with adverse outcomes that include organ dysfunction and death [065].

Pancreatitis Outcome Prediction (POP) score

Another scoring system for predicting outcome in acute pancreatitis, the Pancreatitis Outcome Prediction (POP) score, was developed using data from a retrospective cohort of 2462 patients at the time of admission to the ICU. The POP score is a good predictor of death among patients with severe acute pancreatitis. However, this score has yet to be validated prospectively [065].

Modified CT severity index (MCTSI)

The purpose of this study was to compare the modified CT severity index (MCTSI) with the CT severity index (CTSI) regarding assessment of severity parameters in acute pancreatitis (AP). Both CT indexes were also compared with the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) index. Of 397 consecutive cases of AP, 196 (49 %) patients underwent contrast-enhanced CT (n=175) or MRI (n=21) within 1 week of onset of symptoms. Two radiologists independently scored both CT indexes. Severity parameters

included mortality, organ failure, pancreatic infection, admission to and length of ICU stay, length of hospital stay, need for intervention, and clinical severity of pancreatitis. Although for both CT indexes a significant relationship was observed between the score and each severity parameter, no significant differences were seen between the CT indexes. Compared with the APACHE II index, both CT indexes more accurately correlated with the need for intervention and pancreatic infection and more accurately diagnosed clinically severe disease (area under the curve, 0.87; 95 % confidence interval 0.82 to 0.92). Interobserver agreement was excellent for both indexes: for CTSI, 0.85 (95 % confidence interval 0.80 to 0.90) and for MCTSI, 0.90 (95 % confidence interval 0.85 to 0.95). No significant differences were noted between the CTSI and the MCTSI in evaluating the severity of AP. Compared with APACHE II, both CT indexes more accurately diagnose clinically severe disease and better correlate with the need for intervention and pancreatic infection [068].

Contrast-enhanced ultrasound (CEUS)

To investigate the ability of contrast-enhanced ultrasound (CEUS) in the assessment of acute pancreatitis (AP), as well as its diagnostic accuracy in the evaluation of the severity of pancreatitis a prospective double-blind study was carried out in 33 AP patients from 2007 to 2008. Each patient underwent both CEUS and contrast-enhanced computed tomography (CECT) with the time interval between two examinations less than 72 h. Using CECT as gold standard, the ability of CEUS to diagnose pancreatic necrosis as well as peripancreatic effusion and/or complications, and its diagnostic value in the evaluation of the severity of pancreatitis, were investigated. Balthazar's grading system was used to measure CT and ultrasound severity indices (CTSI and USSI), and the correlation between CTSI and USSI was tested by Spearman's rank correlation coefficient. A strong correlation between CTSI and USSI was found. The sensitivity, specificity, accuracy, positive and negative predictive value of CEUS in the diagnosis of pancreatic parenchyma necrosis were 90, 95, 94, 90 and 95 percent, in the diagnosis of peripancreatic effusion and/or complications were 83, 100, 93, 100 and 91 percent, and in the diagnosis of severe pancreatitis were 97, 67, 94, 97 and 67 percent, respectively. CEUS has shown to be of clinical value in the assessment of pancreatic necrosis as well as peripancreatic complications in AP and has a high diagnostic accuracy in the evaluation of the severity of pancreatitis [069].

Single laboratory tests

Hematocrit

A key advantage of using laboratory tests to determine prognosis is the potential to monitor a patient's initial response to treatment. For patients with acute pancreatitis, initial treatment primarily consists of fluid resuscitation. Several routine laboratory tests have been proposed as possible predictors of outcome: serum hematocrit, serum creatinine and blood urea nitrogen levels. Results of several small single-centre studies in the late 1990s and early 2000s suggested that an elevated hematocrit or "hemoconcentration" at admission was a predictor of pancreatic necrosis. Unfortunately, the accuracy of hematocrit as a prognostic indicator of necrosis was not confirmed in several subsequent external validation studies [065].

Recent data suggest that serial measurement of blood urea nitrogen levels is the most useful routine laboratory test for determining risk of death. Objective assessment of acute pancreatitis (AP) is critical to help guide resuscitation efforts. It was validated serial blood urea nitrogen (BUN) measurement for early prediction of mortality and developed an objective BUN-based approach to early assessment in AP. It was performed a secondary

analysis of 3 prospective AP cohort studies. Meta-analysis and stratified multivariate logistic regression adjusted for age, gender, and creatinine levels were calculated to determine risk of mortality associated with elevated BUN level at admission and rise in BUN level at 24 hours. The accuracy of the BUN measurements was determined by area under the receiver operating characteristic curve (AUC) analysis compared with serum creatinine measurement and APACHE II score. A total of 1043 AP cases were included in analysis. In pooled analysis, a BUN level of 20 mg/dL or higher was associated with an odds ratio (OR) of 4.6 (95 % confidence interval 2.5 to 8.3) for mortality. Any rise in BUN level at 24 hours was associated with an OR of 4.3 (95 % confidence interval 2.3 to 7.9) for death. Accuracy of serial BUN measurement was comparable to that of the APACHE II score in each of the cohorts. A BUN-based assessment algorithm identified patients at increased risk for mortality during the initial 24 hours of hospitalization. It was confirmed the accuracy of BUN measurement for early prediction of mortality in AP and developed an algorithm that may assist physicians in their early resuscitation efforts [070].

C-reactive protein

Several markers of systemic inflammation have also been studied as potential biomarkers to help predict the outcome of acute pancreatitis. The most widely available and well studied is the acute-phase reactant, C-reactive protein. Several observational studies have shown that C-reactive protein levels peak on day three after the start of symptoms and have their greatest prognostic value 48 hours after the start of symptoms. Unfortunately, this timeline limits the usefulness of measuring C-reactive protein levels during the initial treatment phase of acute pancreatitis [065].

Procalcitonin et al

Procalcitonin, polymorphonuclear elastase, and interleukins 6 and 8 have each been shown to have a high degree of accuracy in several prospective observational cohort studies. Although potentially valuable for investigational purposes, none of these parameters is widely available for routine clinical use. Markers of protease activation have also been extensively studied as early predictors of outcome in acute pancreatitis. The most well established is urine trypsinogen-activation peptide, which has been shown to be both an accurate and reliable early prognostic indicator [065].

Visfatin

Adipocytes of peripancreatic and intrapancreatic adipose tissue secrete adipocytokines such as leptin, adiponectin, and resistin. For resistin, a role as an early predictor of peripancreatic necrosis and clinical severity in acute pancreatitis has been reported. It was the aim of this study to investigate whether the adipocytokine visfatin is able to serve as an early marker predicting peripancreatic necrosis and clinical severity. A total of 50 patients (20 females and 30 males) with acute pancreatitis were included in this noninterventional, prospective, and monocentric cohort study on diagnostic accuracy. Clinical severity was classified by the Ranson score and APACHE-II (Acute Physiology and Chronic Health Evaluation II) score. Pancreatic and peripancreatic necrosis were quantified by the computed tomography-based Balthazar score, the Schroeder score, and the pancreatic necrosis score. Visfatin was measured at admission and daily for 10 days by enzyme-linked immunosorbent assay (ELISA). Visfatin values were significantly and positively correlated with clinical severity (APACHE-II score and Ranson score) and with clinical end points such as death and need for interventions. Admission visfatin levels were significantly elevated in patients with higher pancreatic and extrapancreatic necrosis scores. It was shown by receiver operator characteristics that admission visfatin concentration provides a positive predictive value of 93 percent in predicting the extent of peripancreatic necrosis (area under the curve (AUC): 0.89, sensitivity: 93 %, specificity: 82 %, likelihood ratio: 5.1, post-test probability: 93%) by using a

cutoff value of 1.8 ng/mL. It was concluded that admission visfatin concentration serves as an early predictive marker of peripancreatic necrosis and clinical severity in acute pancreatitis. Visfatin may have potential for clinical use as a new and diagnostic serum marker [071].

Cell-free DNA in plasma and serum

Early identification of patients with acute pancreatitis is critical because timely treatment reduces morbidity and mortality but remains one of the major problems in practice. Cell-free (circulating) DNA in serum and plasma has been investigated as a diagnostic tool in chronic diseases and is already applied in prenatal diagnostics. It also was shown to be a predictive marker for severity and mortality in stroke, myocardial infarction, trauma, and sepsis. It was recently shown, in a small, carefully selected population of AP patients, that cell-free DNA can be a good predictor of disease on the first day after admission. Adult patients diagnosed with acute pancreatitis, regardless of etiology, were considered while patients with terminal illnesses and in whom pancreatitis was not primary diagnosis were excluded. One hundred four patients agreed to participate. During hospital stay, 33 (32 %) met the criteria for severe AP, whereas the other 71 (68 %) had mild disease. There were no significant differences in age or gender distribution, or etiology between patients with mild and severe disease. Thirteen (39 %) patients with severe AP were admitted to the intensive care unit (ICU) immediately from the emergency department. Another 15 (45 %) were transferred to the ICU from wards later during their hospitalization (1-6 days), whereas 5 patients fulfilling criteria for severe AP were not treated in the ICU. Both plasma and serum samples were taken on the first day after admission. For all patients, Ranson score was determined in the first 2 hospital days. C-reactive protein was measured on the first 2 days to be evaluated as predictor of severity. The APACHE II score was calculated during the first 24 hours and later in the case of disease progression. Severe pancreatitis, organ failure, and presence of local complications were defined according to the Atlanta 1992 criteria. On the first day after admission, patients who had mild AP had significantly lower levels of free DNA compared with patients who would develop severe disease, in both plasma and serum samples. Median plasma free DNA level measured in patients with mild AP was 0.144 ng/KL, whereas for severe patients, it was 0.593 ng/KL. For serum samples, this difference was a bit smaller: free DNA level for patients with mild disease was 0.230 ng/KL, and that for patients with severe disease was 0.623 ng/KL. Because the primary goal of the study was to test the levels of free DNA as marker for predicting severity of AP, receiver operating characteristic curves were created from the results for both plasma and serum free DNA levels. Results showed that plasma free DNA levels differentiate between patients with mild and severe AP with great sensitivity and specificity (91 % and 89 %, respectively). The source of free circulating DNA in acute conditions is not clearly defined, although cell death is probably the primary source. Our results suggest that DNA quantification could be used as an early marker of severity in AP [072].

OTHER ASPECTS OF ACUTE PANCREATITIS

Epidemiology

A nationwide epidemiological survey was conducted to estimate the number of patients treated for acute pancreatitis (AP) in 2007 in Japan and to clarify the clinicoepidemiological features of AP. In the first survey, a simple questionnaire was used to inquire about the number of patients with AP who visited the hospital in the year 2007. This questionnaire was directly mailed to the heads of 3027 facilities. The second questionnaire was forwarded to those facilities from which patients with AP were reported on the first questionnaire. The estimated total number of patients treated for AP in 2007 was 57,560 (95 % confidence

interval, 48,571 to 66,549), with an overall prevalence rate of 45 per 100,000 population. The sex ratio (male-female) of the patients was 2.0, with a mean age of 57 years in men and 65 years in women. Alcoholic AP was most common in men and gallstone AP in women. The overall mortality rate of AP was 1.9 percent and, in severe cases, 8.0 percent. The number of patients with AP increased about 3-fold during this decade (19,500 in 1998 to 57,560 in 2007), and the mortality rate of AP was reduced from 7.4 percent in 1998 and 2.9 percent in 2003 to 1.9 percent in 2007 [073].

Economical impact

The economic impact of pancreatitis is substantial. A recent US study used data from a variety of government sources to determine the inpatient, outpatient, and long-term care costs for digestive disorders. The total estimated costs of pancreatitis for non-federal institutions and physicians in 2004 were USD 3.7 billion. The number of hospital admissions and ambulatory visits in which pancreatitis was the first-listed diagnosis were 277,000 and 475,000, respectively. Among all digestive disorders, pancreatitis ranked eighth in overall health care costs to society and seventh in hospital admissions and charges. Another study using the National Inpatient Sample estimated the number of hospital discharges from nonfederal US hospitals with a primary diagnosis of acute pancreatitis in 2003 to be 225,600 and the direct medical costs associated with these to be USD 2.2 billion. Assuming that alcohol accounts for about 25 to 30 percent of all cases of AP and 50 percent of all cases of CP, about 40 percent of these costs are likely to be alcohol-related [074].

High volume hospitals

One study aimed to investigate the relationship between hospital volume and clinical outcome in patients with acute pancreatitis, using a Japanese national administrative database. A total of 7007 patients with acute pancreatitis were referred to 776 hospitals in Japan. Patient data were corrected according to the severity of acute pancreatitis to allow the comparison of risk-adjusted in-hospital mortality and length of stay in relation to hospital volume. Hospital volume was categorized based on the number of cases during the study period into low-volume (<10 cases), medium-volume (10-16 cases), and high-volume hospitals (HVHs, >16 cases). Increased hospital volume was significantly associated with decreased relative risk of in-hospital mortality in both patients with mild and those with severe acute pancreatitis. The odds ratios for HVHs were 0.42 (95 % confidence interval 0.23 to 0.79) and 0.34 (95 % confidence interval 0.14 to 0.83), respectively. Hospital volume was also significantly associated with shorter length of stay in patients with mild acute pancreatitis. The unstandardized coefficient for HVHs was -0.978 days (95 % confidence interval -1.909 to -0.048). The study demonstrated that hospital volume influences the clinical outcome in both patients with mild and those with severe acute pancreatitis [075].

Register studies

National patient registers are powerful tools in epidemiological research and healthcare administration. As the level of reliability of diagnoses that are partly based on clinical signs, such as acute pancreatitis, may be low, the reliability of discharge diagnoses in these registers needs to be validated. The main aim of one study was to validate the diagnosis coding for acute pancreatitis in the Swedish National Patient Register. It was randomly sampled 650 admissions of all patients registered in the Swedish National Patient Register with acute pancreatitis or other nonmalignant pancreatic disorders as the main diagnosis in 2007 and 1998, and as the secondary diagnosis in 2007. The medical records for these

admissions were reviewed. It was analyzed the concordance between the coding of acute pancreatitis in the Swedish National Patient Register and criteria based on internationally accepted diagnostic standards. It was received 603 medical records for manual review. Among the 530 patients with a diagnosis of acute pancreatitis in the Swedish National Patient Register, 442 (83 %) were, after review, defined as definitive acute pancreatitis, 80 (15 %) as probable acute pancreatitis, and 8 (2 %) as no acute pancreatitis. There were no significant differences in the reliability of the diagnosis with regard to gender, age, time period or whether the patient had been treated at a county or university hospital. Among the 73 patients registered with a non-malignant pancreatic disorder other than acute pancreatitis, the number of false-negative cases of acute pancreatitis was 23 (32 %). They were mainly found among patients registered with a diagnosis of chronic pancreatitis. It was concluded that the Swedish National Patient Register is highly reliable as regards correct coding of acute pancreatitis. However, there seems to be a non-negligible share of false-negative cases of acute pancreatitis among patients registered with a diagnosis of chronic pancreatitis [076].

Pathogenesis

There is an unacceptably high mortality in acute pancreatitis, which is due to the lack of specific treatments for the disease. A major reason stated to account for the inability to develop effective treatments is that there are multiple pathobiologic pathways activated in the acinar cell mediating pancreatitis making it difficult to choose molecular targets for therapeutic strategies. However, this reasoning limits opportunities for therapeutic development because it does include another important participant in pancreatitis – the pancreatic duct cells. The most recent advance in pancreatitis research is that depletion of both glycolytic and oxidative ATP synthesis is a common event in both acinar and ductal cells. Although ATP has a very short half-life in the blood and is hydrolysed to ADP, there is clear evidence that encapsulating ATP into liposomes can effectively drive ATP into the cells which can be effective in protecting them from necrosis. In one review it was examined the effects of different insults associated with pancreatitis on both the acinar and ductal components of the exocrine pancreas pointing out the role of the ductal epithelial responses in both attenuating and increasing the severity of pancreatitis. In addition, it was proposed that exogenous ATP administration may restore ductal and acinar function providing therapeutic benefit [077].

Influence of obesity

It is generally accepted that there is a correlation between obesity and poor outcome in acute pancreatitis (AP); however, the relationship between overweight and the prognosis of AP is unknown. The aim of one study was to determine the correlation between overweight and the prognosis of AP. MEDLINE and PubMed were searched using the terms “acute pancreatitis”, “obesity”, “overweight”, and “body mass index” (BMI). All prospective clinical studies correlating BMI and AP were included. Obesity and overweight were defined as BMI ≥ 30 and from 25 to 30, respectively. A meta-analysis was performed with the endpoints severe AP (SAP), local complications, systemic complications, and mortality. Eight studies including 939 patients were found. The incidence rates of SAP (OR 2.48, 95 % confidence interval 1.34 to 4.60), local complications (OR 2.58, 95 % confidence interval 1.20 to 5.57), and mortality (OR 3.81, 95 % confidence interval 1.22 to 11.83) were increased in overweight patients with AP. No difference was detected in the incidence of systemic complications between the normal-weight and overweight patients (OR 1.62, 95 % confidence interval 0.76 to 3.43). In addition, the correlation between obesity and poor prognosis was again confirmed [078].

Immunology

Acute pancreatitis is a form of inflammation with clinical features ranging from pancreatic inflammation to fatal systemic manifestations. The aim of this study was to clarify changes in lymphocyte subsets and alterations in the functioning of natural killer (NK) cells. Forty-five patients were enrolled into the study; 35 with acute pancreatitis and systemic inflammatory response syndrome (SIRS) and 10 healthy subjects. Blood was sampled early from all patients. Blood immune cells were studied on days 1 and 4 by flow cytometry. Tumor necrosis factor-alpha (TNF α) and interleukin (IL)-6 were estimated from supernatants of NK cells before/after stimulation with lipopolysaccharide (LPS). Apoptosis in patients was significantly different on days 1 and 4 compared with controls. Apoptosis of CD4(+) lymphocytes was significantly correlated with the days to resolution of SIRS. Significant differences were observed in TNF α -alpha and IL-6 on day 1 with/without LPS stimulation between patients and healthy individuals. Significantly increased levels of TNF-alpha and IL-6 were found after LPS stimulation compared with unstimulated supernatants in day 1. It was concluded that NK cells altered their secretory status when stimulated with LPS. This finding could be explained by the cellular reprogramming of NK cells in the field of acute pancreatitis and SIRS [079].

Tissue factor

Being a central link between inflammation and coagulation, tissue factor (TF) and its inhibitor (TFPI) might be associated with the severity of acute pancreatitis (AP) and the development of organ failure (OF). One study comprised 9 severe AP patients with OF and 24 reference patients (11 mild AP and 13 severe AP without OF). Plasma samples were collected on admission. TF-induced thrombin generation in plasma samples was studied using the thrombogram method. In vivo thrombin generation was estimated by prothrombin fragment F1+2. Free and total TFPI levels were measured. To evaluate coagulation status the activated partial thromboplastin time, prothrombin time, platelet count, D-dimer, fibrinogen, antithrombin (AT) 3 and protein C (PC) were determined. There was no significant difference in F1+2 levels between the patient groups. Patients with severe AP tended to show low platelet counts, PC and AT3 levels, and high D-dimer levels. In 11 patients the standard TF stimulation did not trigger thrombin generation in the thrombogram. All deaths occurred in these patients. Free TFPI levels and free/total TFPI ratios were significantly higher in these patients and in non-survivors. It was concluded that failure of TF-initiated thrombin generation in the thrombogram assay explained by high levels of circulating free TFPI may be associated with OF and mortality in AP [080].

Diagnostics

Lipase

The objective was to investigate the use of serum lipase levels >10,000 U/L as a tool for predicting the etiology of acute pancreatitis (AP) and to further address the relationship between lipase elevation and disease severity. It was compared patients with AP and serum lipase >10,000 U/L (HL) with patients with AP and lower serum lipase levels (855-10,000 U/L). The etiology and severity of AP were recorded. Differences between groups were calculated. Of the 114 patients in the HL group, the common etiologies of AP were biliary (68 %), iatrogenic trauma (14 %), and idiopathic (10 %). Only one patient had alcoholic AP. Conversely, the common etiologies of AP in the 146-patient comparison group (lipase 855-10,000 U/L) were broader: biliary (34 %), idiopathic (23 %), alcohol (14 %), and iatrogenic trauma (10 %). Biliary AP was twice as common in the HL group whereas alcoholic AP was

significantly less common. The positive predictive value (PPV) for biliary AP of lipase >10,000 U/L was 80% whereas the negative predictive (NPV) for alcoholic AP was 99%. No difference between groups was observed in the severity markers including ICU admission, length of hospital stay, complications, or mortality. It was concluded that in AP a serum lipase of >10,000 U/L at presentation is a useful marker and portends a biliary etiology while virtually excluding alcoholic AP. Therefore, if ultrasonography is negative for stones in this population, these data suggest workup with MRCP or EUS is warranted to evaluate for microlithiasis or sludge given the high likelihood of occult stone disease in these individuals [081].

D-dimer

The aim of one study was to investigate the d-dimer in acute pancreatitis and its associations with triglyceride (TG). The d-dimer was measured in 45 patients with mild acute pancreatitis, 43 patients with severe acute pancreatitis, and 45 healthy controls. Eighty-eight patients were divided into high and low TG groups based on their TG levels. Twenty outpatients with serumal TG levels higher than 5.65 mM were chosen as hypertriglyceridemia controls. It was investigated whether there were any correlations between the d-dimer levels and serumal TG in acute pancreatitis. In 45 patients with mild acute pancreatitis, the d-dimer increased to approximately 2 times over the reference value, whereas in 43 patients with severe acute pancreatitis, the d-dimer level increased to 6 times above the limit; the difference was significant. Both TG and acute pancreatitis could cause an elevation of the d-dimer level, in which TG takes a more important role. The increase in the d-dimer was also directly related to the severity of acute pancreatitis. Plasma concentrations of the d-dimer increase in acute pancreatitis. The increase in TG is probably the main cause of the d-dimer elevation in patients with acute pancreatitis [082].

Trypsinogen 2

Trypsinogen 3 is a minor trypsinogen isoform in the pancreas. In contrast with trypsin 1 and 2, trypsin 3 degrades pancreatic secretory trypsin inhibitor, which may lead to an excess of active trypsin and acute pancreatitis (AP). It was developed an immunoassay for trypsinogen 3 and studied whether an assay of serum trypsinogen 3 is of clinical utility in the diagnosis of AP. Monoclonal antibodies were generated using recombinant human trypsinogen 3 as the antigen and used to establish a sandwich-type immunoassay. It was analyzed serum trypsinogen 3 concentrations in 82 patients with AP and 63 patients with upper abdominal pain (controls). The reference interval was determined using serum samples from 172 apparently healthy individuals. The measuring range of the trypsinogen 3 assay was 1.0-250 µg/L. Intra- and interassay CVs were <11 percent, and cross-reactivity with other trypsinogen isoenzymes was <0.1 percent. The median trypsinogen 3 concentration in serum from healthy individuals was <1.0 µg/L, and the upper reference limit was 4.4 µg/L. It was observed increased trypsinogen 3 concentrations in patients with mild (median 9.5 µg/L) and severe (15.0 µg/L) AP; in both groups, the concentrations were significantly higher than in controls (median <1.0 µg/L). In ROC analysis, the area under the curve of trypsinogen 3 for separation between AP and controls was 0.90. It was established for the first time a specific immunoassay for trypsinogen 3 using monoclonal antibodies. Patients with acute pancreatitis were found to have increased serum concentrations of trypsinogen 3. The availability of this assay will be useful for studies of the clinical utility of trypsinogen 3 [083].

Imaging

To evaluate imaging utilization trends in patients with acute pancreatitis (AP) and to assess independent predictors of radiology usage in relation to patient outcomes institutional review board approval was obtained for this HIPAA-compliant study; written informed consent was

waived. AP-related radiologic studies in 252 patients admitted for AP between 2005 and 2007 were collected during and for a 1-year period after hospitalization. Clinical data were collected from patients' medical records, while imaging data were obtained from the radiology information system. Linear regression models were used to investigate predictors and time trends of imaging utilization, after adjustment for confounders. Patient outcomes, measured by using mortality, intensive care unit admission, need for surgical intervention, organ failure, and persistent systemic inflammatory response syndrome, were evaluated by using logistic regression. Mean utilization was 10 radiologic studies per patient (95 % confidence interval 8 to 12), with relative value unit (RVU) of 8 (95 % confidence interval 6 to 9). Utilization was highest on day 0, declining rapidly by day 4; 53 percent of imaging occurred during initial hospitalization. Chest radiography (38 %) and abdominal computed tomography (CT) (17 %) were the most commonly performed studies. Patients with longer hospital stay, higher Acute Physiology and Chronic Health Evaluation II score, higher pain levels, drug-induced AP, and prior episodes of AP underwent significantly more radiologic studies. After adjustment for confounders, a 2.5-fold increase in the use of high-cost (CT and magnetic resonance imaging) examinations and a 1.4-fold increase in RVUs per case-mix-adjusted admissions were observed during the 2.5-year study period. This increased use was not associated with improvement in patient outcomes. Acute pancreatitis severity explained substantial variation in imaging utilization. After case-mix adjustment for severity and other patient level factors, there was still increasing use over the course of time without notable improvement in patient outcomes [084].

Dynamic CT

The aim of one study was to assess severe acute pancreatitis (SAP) with Ranson score and CT scan. Between 2000 and 2005, all patients who had first-time diagnosis of acute pancreatitis, acute pancreatitis as the primary admitting diagnosis, and contrasted-enhanced computed tomography (CE-CT) were retrospectively reviewed. Ninety-eight patients that met the present study criteria were identified. Of these patients, 27 were defined as SAP by using Ranson criteria and/or CE-CT. Within SAP group, factors showing significance in the patients that had a Ranson score between ≥ 3 and < 3 were age and biliary tract stone. It was concluded that the incidence of severe acute pancreatitis in the investigated hospital was 28 percent. Biliary disease and alcohol abuse together accounted for 82 percent of severe acute pancreatitis patients [085].

Gallstone-induced acute pancreatitis

Common biliary duct stones

Treatment of common bile duct stones has changed. Open surgery has gradually been replaced by endoscopic and laparoscopic procedures. The aims of one study were to see how common bile duct stones have been treated in Sweden, to establish whether there were differences in morbidity and mortality between these approaches, and to identify factors influencing mortality. All persons undergoing inpatient common bile duct exploration or endoscopic retrograde cholangiopancreatography (ERCP) during 1965-2009 in the Swedish Hospital Discharge Registry, but without a diagnosis of malignancy in the Swedish Cancer Registry, were included. The outcome death was identified by cross-linkage to the Causes of Death Registry. Registry data on possible risk factors for mortality were collected. A total of 126 885 procedures were performed in 110 119 patients. Open surgery was initially the only available method, but during the 1990s ERCP became predominant. Later, laparoscopic bile duct clearance became an established but uncommon method. A 90-day mortality rate of 0.2 per cent after open surgery, 0.8 percent after ERCP, 0 percent after laparoscopic exploration and 0.7 percent after combined procedures was recorded. After adjustment for confounding, there was no difference in mortality between open surgery and ERCP. Biliary reintervention

within 90 days was identified as a risk factor for death, whereas a concomitant diagnosis of pancreatitis reduced the risk. It was concluded that the laparoscopic technique had the lowest mortality and morbidity rates. After adjustment for confounding factors, there was no difference in mortality after open surgery and ERCP. The favourable outcome for laparoscopy may have been due to selection bias, owing to treatment of younger, healthier subjects with less severe disease [086].

Timing of cholecystectomy after mild biliary pancreatitis

The aim of one study was to evaluate recurrent biliary events as a consequence of delay in cholecystectomy following mild biliary pancreatitis. Between 2004 and 2007, patients with acute pancreatitis were registered prospectively in 15 Dutch hospitals. Patients with mild biliary pancreatitis were candidates for cholecystectomy. Recurrent biliary events requiring admission before and after cholecystectomy, and after endoscopic sphincterotomy (ES), were evaluated. Of 308 patients with mild biliary pancreatitis, 267 were candidates for cholecystectomy. Eighteen patients underwent cholecystectomy during the initial admission, leaving 249 potential candidates for cholecystectomy after discharge. Cholecystectomy was performed after a median of 6 weeks in 188 patients (76 %). Before cholecystectomy, 34 patients (14 %) were readmitted for biliary events, including 24 with recurrent biliary pancreatitis. ES was performed in 108 patients during the initial admission. Eight (7 %) of these patients suffered from biliary events after ES and before cholecystectomy, compared with 26 (18 %) of 141 patients who did not have ES (risk ratio 0.51, 95 % confidence interval 0.27 to 0.94). Following cholecystectomy, eight (4 %) of 206 patients developed biliary events after a median of 31 weeks. Only 142 (53 %) of 267 patients were treated in accordance with the Dutch guideline, which recommends cholecystectomy or ES during the index admission or within 3 weeks thereafter. It was concluded that a delay in cholecystectomy after mild biliary pancreatitis carries a substantial risk of recurrent biliary events. ES reduces the risk of recurrent pancreatitis but not of other biliary events [087].

Alcohol-induced acute pancreatitis

Clinical observation has defined the medical profile of alcoholic pancreatitis, but its low incidence and prevalence has limited characterizing the disease at a population level, the contribution of environmental exposures, and a clear picture of its natural history. Recent studies have defined the impact of alcohol use and smoking on disease risk, and a threshold for alcohol consumption has been identified. Recurrent attacks of acute pancreatitis have been linked with continued alcohol consumption, and aggressive alcohol intervention has been shown to decrease recurrence. Progression from alcoholic acute pancreatitis to chronic pancreatitis is now believed to occur infrequently, and factors associated with progression have been identified. Alcoholic pancreatitis reduces lifespan in these patients, and the economic impact of pancreatitis is substantial [088].

Initial observations from the 1960s to the 1990s, mainly from specialized centers, clarified the clinical profile and natural history of alcoholic chronic pancreatitis (CP). Recent studies have used a population-based or multicenter approach to address many unanswered questions and provide a new perspective on the epidemiology of alcoholic pancreatitis. These reports have described the distribution of pancreatitis at a population level and its economic impact, and have better defined the relationship between environmental exposure with risk, recurrence, progression, and survival. Unfortunately no universally accepted criteria exist to assign alcohol as an etiology of a patient's pancreatitis. Experts have used definitions varying from consumption of over 50 to 80 g (i.e. 4 to 7 drinks/day) with or without a minimum drinking duration. An international consensus panel defined alcoholic CP based on typical clinical history, threshold alcohol consumption (80 g or more of alcohol for a few years

in males, less in females), and morphological evidence of CP on imaging studies or histology. Overall survival in patients with alcoholic pancreatitis is significantly lower compared with the background population, and most patients die from causes unrelated to pancreatitis. The natural history of alcoholic CP is distinctly different from idiopathic CP, especially the late-onset type. Patients with alcoholic etiology have more symptomatic disease characterized by a higher frequency of pain, attacks of acute or recurrent AP, or complications (e.g. pseudocysts) [074].

In observational studies from the 1960s to the 1990s, alcohol was cited as the predominant etiology of CP (60-90 %). It is noteworthy that although alcohol continues to be the dominant etiology, the proportion of patients in whom alcohol is attributed as a single or contributing etiologic factor has been lower in recent multicenter studies (about 50 %). In the United States, two large studies have reported on alcohol consumption in patients with chronic pancreatitis. Among 448 CP patients evaluated at the Mayo Clinic from 1976 to 1982, Lamer et al found that 18 percent were lifetime abstainers, 18 percent consumed moderate amounts of alcohol (< 50 g/d), and 56 percent were heavy drinkers (> 50 g/d), whereas alcohol consumption was unknown in nearly 8 percent patients. Patients who consumed more than 50 g/d were considered to have alcoholic etiology. A recent multicenter US study prospectively enrolled 540 CP patients from 2000 to 2006 from 19 centers with specific interest in pancreatic diseases. Physicians considered alcohol as the sole or contributing cause of CP in about 45 percent patients. However, the spectrum of disease at a population level may be quite different from those evaluated at specialized centers: it is likely that patients referred to specialized centers include those for whom no specific etiology for CP could be determined or who have more symptomatic or complicated disease. Moreover, cross-sectional imaging (CT and MRI) has become highly sensitive to detect morphological changes in the pancreas, thereby leading to earlier diagnosis. Third, the proportion of females in the patient cohort would affect the overall proportion of patients with alcohol etiology; the lower prevalence of alcohol etiology in the US studies compared with the European centers could be due in part to a higher proportion of females. Whereas the peak age for presentation of alcoholic pancreatitis is uniformly 40 to 60 years, incidence differs based on gender, race, and geographic distribution. Lankisch et al determined that at equal levels of consumption, the rates of alcoholic pancreatitis are similar for both genders. Thus, overrepresentation of males among patients with alcoholic pancreatitis reflects a higher prevalence of alcohol consumption than gender-based differences in susceptibility [074].

The prevalence of changes attributable to chronic pancreatitis in autopsies of alcoholic individuals is much higher than those observed in clinical studies, suggesting that subclinical damage to the pancreas is more common in alcoholic subjects than is reported. A recent study assessed histology in 7541 subjects – of whom 620 (8 %) had a diagnosis of alcoholism – and showed a prevalence of CP changes of 14 percent. In the same study, the prevalence of cirrhosis among alcoholics was 30 percent. A high degree of overlap was seen, with 18 percent of patients with cirrhosis also demonstrating CP changes, and, conversely, 38 percent patients with chronic pancreatitis showing cirrhotic changes of the liver. Such concurrent damage in alcoholic subjects suggests that at least some factors and/or mechanisms for organ damage are similar across organs [074].

Kristiansen et al evaluated the probability of receiving a pancreatitis diagnosis in a cohort of about 18,000 men and women followed for a mean of 20 years. The risk of any pancreatitis among self-reported abstainers at the time of initial evaluation was 1.3 percent (0.89 % AP, 0.4 % CP) and among individuals who consumed 35 or more drinks/week (5 or more drinks/day) was 2.5 percent (1.6 % acute, 1.3 % chronic). Overall, risk of pancreatitis increases only with higher alcohol exposure than is seen with other diseases. For example, the estimated threshold for increased risk is about 2 drinks/day for heart and chronic liver diseases. Drinking behaviors also can vary widely over an individual's lifetime [074].

Acute and chronic pancreatitis is a major complication of alcohol abuse. The pancreas can metabolize ethanol via oxidative pathway involving the enzymes – alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) as well as the nonoxidative pathway. Human pancreas tissue contains various ADH isoenzymes and possesses also ALDH activity. In one paper it was measured the activity of alcohol dehydrogenase isoenzymes, and aldehyde dehydrogenase in the sera of patients with acute and chronic pancreatitis. Serum samples were taken for routine biochemical investigation from 46 patients suffering from acute pancreatitis and 32 patients with chronic pancreatitis. Total ADH activity was measured by photometric method with p-nitrosodimethylaniline (NDMA) as a substrate and ALDH activity by the fluorometric method with 6-methoxy-2-naphtaldehyde as a substrate. For the measurement of the activity of class I isoenzymes we employed the fluorometric methods, with class-specific fluorogenic substrates. The activity of class III alcohol dehydrogenase was measured by the photometric method with n-octanol and class IV with m-nitrobenzaldehyde as a substrate. A statistically significant increase of class III alcohol dehydrogenase isoenzymes was found in the sera of patients with acute and chronic pancreatitis. The median activity of this class isoenzyme in the patients group increased about 35% in the comparison to the control level. The total alcohol dehydrogenase activity was also significantly higher (24 %) among patients with pancreatitis than healthy ones. The activities of other tested ADH isoenzymes and total ALDH were unchanged. The activity of the class I ADH isoenzyme was significantly higher in the sera of heavy drinkers with pancreatitis. It was concluded that the increase of the activity of class III alcohol dehydrogenase isoenzyme in the sera of pancreatitis patients seems to be caused by the release of this isoenzyme from damaged pancreatic cells [089].

Smoking as a risk factor

The environmental factor that has gained the most attention as a potential contributor to CP risk is smoking. Since the first report linking smoking and CP about 30 years ago, several epidemiology studies using different study designs have firmly established smoking as a risk factor for pancreatitis. Lankisch et al noted that smoking increases the risk of progression from acute to chronic by about fourfold [074].

Post-ERCP-pancreatitis

Placement of prophylactic pancreatic stents (PPS) is a method proven to reduce the rate and severity of postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) in high-risk patients; however, PPS do not eliminate the risk completely. Early PPS dislodgement may occur prematurely and contribute to more frequent or severe PEP. A total of 27,176 ERCP procedures from 1994 to 2007 for PPS placement in high-risk patients were analyzed. Patient and procedure data were analyzed to assess risk factors for PEP, and to evaluate the severity of pancreatitis, length of hospitalization and subsequent complications. Timing of stent dislodgment was assessed radiographically. PPS were placed in 7661 patients. Of these, 580 patients (8 %) developed PEP, which was graded as mild in 460 (6 %), moderate in 87 (1 %) and severe in 33 (0.5 %). Risk factors for developing PEP were not different in patients who developed moderate PEP compared with those with severe PEP. PPS dislodged before 72 h in seven of 59 (12 %) patients with moderate PEP and five of 27 (19 %) patients with severe PEP. The mean (\pm SD) length of hospitalization in patients with moderate PEP with stent dislodgement before and after 72 h was 7.4 ± 1.5 days and 8.4 ± 1.2 days, respectively. The mean length of hospitalization in patients with severe PEP whose stent dislodged before and after 72 h were 22 ± 6.1 and 22.2 ± 3.1 days, respectively. It was concluded that early PPS dislodgement was associated with moderate and severe PEP in less than 20 percent of cases and was not associated with a more severe course. Factors

other than ductal obstruction contribute to PEP in high-risk patients undergoing ERCP and PPS placement [090].

Pancreatitis is the most common complication of diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The incidence of clinical post-ERCP pancreatitis is about 5 percent. The authors describe a case of 60-year-old man who developed an unusual focal, instead of usual diffuse pancreatitis after diagnostic ERCP. F-18 FDG PET/CT in 3 days after ERCP detected focal FDG uptake because of pancreatitis, and the diagnosis was confirmed by spontaneous resolution of the lesion on 1-week follow-up PET/CT study [091].

Pancreatitis is the most common major complication of endoscopic retrograde cholangiopancreatography (ERCP). Efforts have been made to identify pharmacologic agents capable of reducing its incidence and severity. The aim of one trial was to determine whether prophylactic nafamostat mesilate, a synthetic protease inhibitor, would reduce the frequency and severity of post-ERCP pancreatitis. A total of 286 patients were randomized to receive either intravenous nafamostat mesilate or placebo 60 minutes before ERCP and for 6 hours after ERCP. A database was prospectively collected by a defined protocol. Standardized criteria were used to diagnose and grade the severity of pancreatitis. The groups were similar with regard to patient demographics and to patient and procedure risk factors for pancreatitis. The overall incidence of pancreatitis was 6 percent. It occurred in 4 (2.8 %) of 143 patients in the nafamostat group and in 13 (9.1 %) of 143 patients in the control group. Pancreatitis was graded mild in 2.1 percent and moderate in 0.7 percent of the nafamostat group and mild in 7.0 percent and moderate in 2.1 percent of the control group. There was no significant difference between the groups in the severity of pancreatitis. It was concluded that prophylactic intravenous nafamostat mesilate reduces the frequency of post-ERCP pancreatitis [092].

Secretin prophylaxis

One study aimed to evaluate whether synthetic secretin is effective in reducing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. It was a single academic medical center, prospective, randomized, double-blind, placebo-controlled trial using secretin (dose of 16 microg) administered intravenously immediately before ERCP. Patients were evaluated for the primary outcome of post-ERCP pancreatitis as diagnosed by a single investigator. A total of 1100 patients were screened, of whom 869 were randomly assigned to receive secretin (n=426) or placebo (n=443) before ERCP and were evaluated after the procedure for efficacy of secretin. The incidence of pancreatitis in the secretin group compared with the placebo group was 36 (8.7 %) of 413 patients versus 65 (15.1 %) of 431 patients, respectively, which was a statistically significant difference. In the subgroup analysis, secretin was highly protective against post-ERCP pancreatitis for patients undergoing biliary sphincterotomy (6/129 vs 32/142), patients undergoing cannulation of the common bile duct (26/339 vs 56/342), and patients not undergoing pancreatic sphincterotomy (26/388 vs 57/403). Analysis of the interaction between these groups reveals that the primary effect of secretin prophylaxis was prevention of post-ERCP pancreatitis in patients undergoing biliary sphincterotomy. It was concluded that synthetic secretin reduces the risk of post-ERCP pancreatitis, particularly in patients in undergoing biliary sphincterotomy [093].

Triglycerid-induced acute pancreatitis

Type 1 hyperlipoproteinemia (T1HLP) in childhood is most often due to genetic deficiency of lipoprotein lipase (LPL) or other related proteins. The aim was to report a case of marked

hypertriglyceridemia and recurrent acute pancreatitis due to the presence of LPL autoantibody in a young girl who was subsequently diagnosed with Sjögren's syndrome. A 9-yr-old African-American girl presented with acute pancreatitis and serum triglycerides of 4784 mg/dl. Strict restriction of dietary fat reduced serum triglycerides, but she continued to experience recurrent pancreatitis. Approximately 18 months thereafter, she developed transient pauciarticular arthritis with elevated serum antinuclear antibody (>1:1280). Minor salivary gland biopsy revealed chronic sialadenitis with a dense periductal lymphocytic aggregate suggestive of Sjögren's syndrome. Genomic DNA was analyzed for LPL, GPIHBP1, APOA5, APOC2, and LMF1. Immunoblotting was performed to detect serum LPL autoantibody. The patient had no disease-causing variants in LPL, GPIHBP1, APOA5, APOC2, or LMF1. Immunoblotting revealed serum LPL antibody. The patient responded to immunosuppressive therapy for Sjögren's syndrome with resolution of hypertriglyceridemia. Unexplained T1HLP in childhood could be secondary to LPL deficiency induced by autoantibodies. Therefore, diagnosis of autoimmune T1HLP should be entertained if clinical features are suggestive of an autoimmune process [094].

In triglyceridaemia-associated pancreatitis, decreasing the serum triglyceride level below 5.65 mmol/L alleviates abdominal pain and is purported to improve outcome. It was analysed hypertriglyceride level normalisation and outcome in a patient cohort of acute pancreatitis. Patients presenting with pancreatitis and hypertriglyceridaemia were assessed. All patients with presenting triglycerides levels >10 mmol/L were assessed for resolution to a level below 5.65 mmol/L at days 3 and 5. Patients with triglyceride levels in excess of 10 mmol/L were treated with either standard supportive therapy or an insulin dextrose infusion. In the period 2001 to 2008, there were 503 admissions of 439 patients with a diagnosis of acute pancreatitis; 26 (6 %) had hypertriglyceridaemia >10 mmol/L at admission. Standard therapy was used in all patients; in 6 patients, it was the sole therapy. A dextrose and insulin infusion was used in 20 cases. On day 3, 7 (32 %) of the measured triglyceride levels had fallen below 5.65 mmol/L and, on day 5, all but 4 (83 %) were <5.65 mmol/L. Three patients died. It was concluded that standard therapy was equivalent to the use of dextrose and insulin in the resolution of hypertriglyceridaemia. The methods to reduce triglyceride levels produce morbidity and mortality rates similar to those attained when alternate lipid-lowering strategies are employed [095].

Drug-induced acute pancreatitis

Azathioprine

Thiopurines are considered first-line immunomodulators for the prevention of relapse in moderate to severe pediatric Crohn's disease (CD). Early introduction of thiopurines was shown in a pediatric trial to maintain steroid-free remission in 90% of patients for 18 months. In the present study we analyzed the tolerance and efficacy of azathioprine (AZA) to maintain remission in a homogenous single-center observational cohort of children with CD. In all, 105 pediatric CD patients (male/female 68/37) were retrospectively evaluated for the efficacy of AZA (doses 1.4-4 mg/kg) to maintain remission at 6, 12, 18, and 24 months of follow-up. Overall, 93 children were included with active disease (pediatric Crohn's disease activity index, PCDAI >30), steroid/enteral-nutrition dependency, or postileocecal resection. Remission was defined as PCDAI ≤10 without steroids. Patients requiring antitumor necrosis factor (TNF) medication, other immunomodulators, or surgery were considered to experience a relapse. Based on PCDAI, steroid-free remission was achieved in 56/93 (60 %), 37/93 (40 %), 31/93 (33 %), and 29/93 (31 %) at visits month (M)6, M12, M18, and M24, respectively. Within the first 4 weeks, AZA was stopped in 10/93 patients due to adverse reactions (pancreatitis, nausea, vomiting, skin reactions, general weakness), or not introduced due to low thiopurine methyl transferase (TPMT) activity (n=3). No neutropenia occurred in patients

with normal TPMT activity. Three infectious episodes were documented requiring temporary AZA suspension. It was concluded that AZA is efficacious in maintaining remission in pediatric CD patients, but to a lesser extent than previously suggested. The majority of patients who are in steroid-free remission at 12 months remained in prolonged remission. Overall tolerance of AZA was excellent [096].

Entecavir

In most cases clinical profile of acute hyperlipidemic pancreatitis is a preexisting lipoprotein abnormality associated to second risk factors such as alcohol abuse, diabetes mellitus or medications that can induce hypertriglyceridemia. It was reported a case of a young male affected by chronic hepatitis B virus infection admitted to Emergency Department due to acute abdominal pain, vomiting and fever. The patient was in antiretroviral treatment with entecavir; moreover he was affected by diabetes mellitus and he presented a past history of alcohol abuse. Laboratory tests demonstrated hyperglycemia, severe metabolic acidosis and hypertriglyceridemia, whereas abdominal computed tomography scan revealed peripancreatic edema: hyperlipidemic pancreatitis was supposed and the patient was admitted to the intensive care unit. Considering its possible role in the pathogenesis of pancreatitis, entecavir was interrupted and total of 3 sessions of plasmapheresis were performed, allowing clinical resolution and prevention of pancreatic damage. The possible pathogenetic role of entecavir is discussed [097].

Isoniazide

Drug-induced acute pancreatitis should be considered in the differential diagnosis of acute abdomen occurring soon after the initiation of antitubercular treatment. Isoniazid-induced pancreatitis is potentially reversible: early recognition and drug withdrawal are warranted in the appropriate clinical setting. It was presented a case of reversible acute pancreatitis after isoniazid treatment of lymph node tuberculosis, followed by the recurrence of pancreatitis upon the reintroduction of the drug [098].

Loperamide

Loperamide, a synthetic agonist of peripheral opiate receptors, is used within doses of 2 to 16 mg daily to treat acute or chronic diarrhea. It was reported a case of loperamide overdose associated with extremely high levels of pancreatic enzymes that normalized within 30 hours. The elevation of pancreatic enzymes caused by loperamide overdose probably results from a combination of 2 mechanisms. Loperamide has been shown to decrease amylase output intraduodenally; as an opiate receptor agonist, it probably causes a spasm at the sphincter of Oddi, the same way as morphine. Second, loperamide, like morphine, is known to inhibit the release of pancreatic polypeptide; the action of pancreatic polypeptide is to suppress the secretion from the exocrine pancreas. Without this regular suppression, there is most likely an increase of exocrine pancreas secretion [099].

L-Asparaginase

L-Asparaginase is an effective drug in childhood acute lymphoblastic leukemia (ALL) and it has become an important component of most childhood ALL regimens with administration in induction, intensification, and maintenance phases of treatment. L-Asparaginase is associated with side effects occurring either in a dose or time-dependent fashion or as hypersensitivity reactions. Some well-known toxicities in asparaginase-containing regimens are hypersensitivity/allergy and thromboembolic events. When asparaginase and steroids are used together, mild hyperlipemia is reasonably common. As some published studies show, this abnormality is often underdiagnosed. Hyperlipemia rarely constitutes a clinical

problem; however, when triglyceride elevation is greater than 1000 mg/dL, the risk of pancreatitis is increased. It was reported a case of a young female presenting with acute severe hypertriglyceridemia (9250 mg/dL) during intensification phase of ALL, with neurologic symptoms but without the development of pancreatitis. She was successfully managed with 1 single run of plasmapheresis [100].

Stigalipitin

Glucagon-like peptide-1-based therapy is gaining widespread use for type 2 diabetes, although there are concerns about risks for pancreatitis and pancreatic and thyroid cancers. There are also concerns that dipeptidyl peptidase-4 inhibitors could cause cancer, given their effects on immune function. It was examined the US Food and Drug Administration's database of reported adverse events for those associated with the dipeptidyl peptidase-4 inhibitor sitagliptin and the glucagon-like peptide-1 mimetic exenatide, from 2004-2009; data on adverse events associated with 4 other medications were compared as controls. The primary outcomes measures were rates of reported pancreatitis, pancreatic and thyroid cancer, and all cancers associated with sitagliptin or exenatide, compared with other therapies. Use of sitagliptin or exenatide increased the odds ratio for reported pancreatitis 6-fold as compared with other therapies. Pancreatic cancer was more commonly reported among patients who took sitagliptin or exenatide as compared with other therapies. All other cancers occurred similarly among patients who took sitagliptin compared with other therapies. These data are consistent with case reports and animal studies indicating an increased risk for pancreatitis with glucagon-like peptide-1-based therapy. The findings also raise caution about the potential long-term actions of these drugs to promote pancreatic cancer [101].

Ischemia-induced acute pancreatitis

A 49-year-old man presented with chest pain and was given a diagnosis of aortic dissection based on computed tomography (CT) findings. Two days later the dissection reached the origin of the celiac artery and there was poor blood flow from the body to the tail of the pancreas and fundus of the stomach wall. Severe acute pancreatitis developed. Endoscopy showed a near-circumferential gastric ulcer in the gastric cardia and we diagnosed ischemic gastropathy. A fistula between the area of infected pancreatic necrosis and the stomach had formed spontaneously and the necrotic tissue was draining into the stomach. His recovery was uneventful [102].

Superior mesenteric artery dissection

Due to increased use and improvements in diagnostic imaging studies, spontaneous isolated superior mesenteric artery dissection (SISMAD), which is a rare vascular event, has been reported to occur on a more frequent basis. Although there have been some anecdotal case reports describing the underlying pathology of SISMAD, the etiology of the majority of SISMAD is still poorly understood. The purpose of this study was to determine the underlying cause of SISMAD. From 2001 to 2010, 51 consecutive patients with SISMAD (symptomatic 39, asymptomatic 12) and 38 patients with combined aortic and superior mesenteric artery dissection (CASMAD) were identified in a single institution by retrospective investigations. Diagnosis was dependent on multi-detector helical computed tomography (CT) scan. To find clinical characteristics of SISMAD, it was compared demographic, clinical, and lesion (site of entry tear, type, length) characteristics between the two groups. To find any flow dynamic abnormalities at the proximal segment of the superior mesenteric artery (SMA), we conducted flow dynamic studies using computational fluid dynamic models. Streamline patterns and wall shear stress distributions were tested with computer simulation models

using three different branching angles of SMA from the abdominal aorta. Compared to CASMAD, SISMAD was more common in men (90 % vs 71 %), less frequently associated with hypertension (31 % vs 66 %), and more frequently associated with intra-abdominal cancers (12 % vs 0 %). In a fluid dynamic study using computational fluid dynamic models, we found abnormal mechanical stresses at the anterior wall around the convex portion of the SMA. It was concluded that development of SISMAD seems to be less likely the result of hypertension or connective tissue disease but more likely due to hemodynamic force caused by convex curvature [103].

Acute pancreatitis during pregnancy

Acute pancreatitis in pregnancy is a rare condition estimated to occur in 1 per 1000 to 1 per 12,000 pregnancies. The most frequent etiology in pregnancy is biliary, followed by hyperlipidemia and/or alcohol abuse. Abdominal ultrasound and endoscopic ultrasound are ideal imaging techniques for diagnosing disease because they have no radiation risk. Computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography should be used with caution. Treatment could be conservative or surgical, and standard algorithms are slightly modified in pregnant women. In the last decades the outcome of acute pancreatitis in pregnancy is much better, and perinatal mortality is less than 5 percent [104].

Pancreatitis is a concerning clinical event during pregnancy, with high morbidity and mortality rates for mother and fetus. Hypertriglyceridemia is considered a rare cause of pancreatitis in pregnancy, with the majority of reported cases being associated with the lipid metabolism disorders. It was reported on a case of hypertriglyceridemia-induced pancreatitis in a woman presenting at 32 weeks of gestational age. Her dyslipidemia was not controlled with diet alone, necessitating medical intervention. Fenofibrate was used successfully. Recurrence of pancreatitis during the pregnancy was avoided, and a healthy neonate was delivered at 35 weeks of gestation. It was concluded that fenofibrate could be used safely and successfully during pregnancy in this case of hypertriglyceridemia-associated pancreatitis refractory to conservative measures [105].

Hepatic artery dissection

It was described a case of hepatic artery dissection in a 65-year-old woman. This is the 22nd reported case of hepatic artery dissection, and the first associated with mild acute pancreatitis. The incidence of this condition may be increasing with rising rates of intervention affecting the biliary system. Recognition may also be increasing with growing use of high-quality radiography. Treatment should prevent rupture and ameliorate cardiovascular risk. Surgery should be considered in patients with complications or those likely to have them in future [106].

Severe acute pancreatitis

The patients with acute pancreatitis are at risk to develop different complications from ongoing pancreatic inflammation. Often, there is no correlation between the degree of structural damage to pancreas and clinical manifestation of the disease. The effectiveness of any treatment is related to the ability to predict severity accurately, but there is no ideal predictive system or biochemical marker. Severity assessment is indispensable to the selection of proper initial treatment in the management of acute pancreatitis. The use of multiparametric criteria and the evaluation of severity index permit us to select high-risk

patients. Furthermore, contrast-enhanced computed tomographic scanning and contrast-enhanced MRI play an important role in severity assessment. The adoption of multiparametric criteria proposed together with morphological evaluation consents the formulation of a discreetly reliable prognosis on the evolution of the disease a few days from onset [107].

Post SAP fungal infection

Intra-abdominal infections of pancreatic or peripancreatic necrotic tissue complicate the clinical course of severe acute pancreatitis (SAP) and are associated with significant morbidity. Fungal infection of necrotic pancreatic tissue is increasingly being reported. The incidence of intra-abdominal pancreatic fungal infection (PFI) varies from 5 to 69 percent. *Candida albicans* is the most frequently isolated fungus in patients with necrotizing pancreatitis. Prolonged use of prophylactic antibiotics, prolonged placement of chronic indwelling devices, and minimally invasive or surgical interventions for pancreatic fluid collections further increase the risk of PFI. Computed tomography- or ultrasound-guided fine-needle aspiration of pancreatic necrosis is a safe, reliable method for establishing pancreatic infection. Amphotericin B appears to be the most effective antifungal treatment. Drainage and debridement of infected necrosis are also critical for eradication of fungi from the poorly perfused pancreatic or peripancreatic tissues where the antifungal agents may not reach to achieve therapeutic levels. Fungal infection adversely affects the outcome of patients with SAP and is associated with increased morbidity, although the mortality rate is not increased specifically because of PFI. Although antifungal prophylaxis has been suggested for patients on broad-spectrum antibiotics, no randomized controlled trials have yet studied its efficacy in preventing PFI [108].

Lung injury in acute pancreatitis

Accurate, early identification of patients at risk for developing acute lung injury (ALI) provides the opportunity to test and implement secondary prevention strategies. Objectives: To determine the frequency and outcome of ALI development in patients at risk and validate a lung injury prediction score (LIPS). In this prospective multicenter observational cohort study, predisposing conditions and risk modifiers predictive of ALI development were identified from routine clinical data available during initial evaluation. The discrimination of the model was assessed with area under receiver operating curve (AUC). The risk of death from ALI was determined after adjustment for severity of illness and predisposing conditions. Twenty-two hospitals enrolled 5,584 patients at risk. ALI developed a median of 2 (interquartile range 1-4) days after initial evaluation in 377 (7 %; 148 ALI-only, 229 adult respiratory distress syndrome) patients. The frequency of ALI varied according to predisposing conditions (from 3 % in pancreatitis to 26 % after smoke inhalation). LIPS discriminated patients who developed ALI from those who did not with an AUC of 0.80 (95 % confidence interval 0.78 to 0.82). When adjusted for severity of illness and predisposing conditions, development of ALI increased the risk of in-hospital death (odds ratio, 4.1; 95% confidence interval, 2.9-5.7). ALI occurrence varies according to predisposing conditions and carries an independently poor prognosis. Using routinely available clinical data, LIPS identifies patients at high risk for ALI early in the course of their illness. This model will alert clinicians about the risk of ALI and facilitate testing and implementation of ALI prevention strategies [109].

Recurrent acute pancreatitis

Recurrent acute pancreatitis is a common clinical problem. Most cases of pancreatitis are identified by a careful history and physical examination. Despite advanced evaluation, the

cause is not apparent in about 10 percent of cases. The etiology of recurrent acute pancreatitis appears to be multifactorial, with genetic and environmental influences playing a significant role. The strength of evidence for certain etiologies is highly variable, and natural history data are limited. Controversy exists regarding the most appropriate diagnostic and therapeutic approach. Recurrent acute pancreatitis often represents a continuum with chronic pancreatitis [110].

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood. The first description of this disorder was made by William Heberden in 1801. In 1837, Johann Schönlein described the association of purpura and joint pain as peliosis rheumatica. It is a rare cause of acute pancreatitis in children. The disease process is usually self-limiting, and most children have a good outcome. It was now reported a 15-year-old girl who presented with acute pancreatitis that is associated with Henoch-Schönlein Purpura. She developed abdominal pain and nausea, which was most severe in her epigastric region. She had no vomiting or diarrhea, no migratory right lower abdominal pain, no radiation pain. The local clinic made the diagnosis of acute appendicitis and gave her emergency appendectomy. The pathological diagnosis was simple appendicitis with appendiceal fecalith. After the operation, the abdominal pain was relieved. However, 3 days later, she developed gross hematuria and again petechial rash on her lower extremities. However, at night of the admission, the patient had a sudden onset of epigastric pain, radiating straight through the midcentral back; the maximum body temperature was 38.5 °C, her blood pressure was 120/80 mm Hg, and her pulse was regular at 90 beats per minute. Physical examination found purpura rash on her lower extremities and feet, moderate epigastric tenderness, percussion tenderness on the kidney region, and diminished bowel sound. There was no hepatosplenomegaly. Because acute pancreatitis was confirmed, the patient was transferred to an intensive care unit for close monitoring. Henoch-Schönlein purpura is a rare cause of acute pancreatitis that can occur before or after the characteristic rash. The first case was reported by Garner in 1972.³ Acute pancreatitis is presumed to be caused by vasculitic involvement of the pancreas. It tends to develop in the first week of the illness but may develop as late as day 45. Although serum amylase levels can be normal in 10 to 15 percent of patients, elevated serum lipase level is also appropriate for early diagnosis. Most cases of HSP pancreatitis are mild in nature but can be complicated with hemorrhage, necrosis, and pseudocyst [111].

Fluid therapy

Fluid resuscitation is a key component of the early management of acute pancreatitis. Current clinical practice guidelines recommend aggressive fluid resuscitation despite limited prospective data. It has now been presented findings from a prospective cohort study that evaluates the relationship between early resuscitation parameters and several important outcome measures. Their findings challenge several of the long held beliefs regarding the benefits of vigorous fluid resuscitation in the early phase of acute pancreatitis. Findings from this study along with several others now suggest that a more tailored approach to resuscitation is needed [112].

Supportive therapy is highlighted as the most important therapeutic strategy by all of the guidelines and reviews on acute pancreatitis (AP). They also recommend early, aggressive fluid therapy. Although aggressive fluid therapy is universally recommended, there remains a paucity of data to support current clinical recommendations. Evidence of the benefit of early, aggressive fluid therapy on the prognosis of AP is derived from indirect data. It has been reported that a high admission hematocrit as an expression of hemoconcentration is

associated with a poor outcome: a higher frequency of pancreatic necrosis and organ failure (OF) has been reported. Failure of admission hematocrit to decrease at 24 h (probably associated with inadequate fluid therapy) is associated with a higher frequency of pancreatic necrosis and OF. Increase in blood urea nitrogen (BUN), also related to blood volume decrease, has been associated with a high mortality rate. However, an association between administration of a great amount of fluid during the initial 24 h and an improved outcome of AP has not been shown in the literature. In a study in patients with a high admission hematocrit who were recruited in two previous studies published by the same group, there was no difference in the incidence of pancreatic necrosis based on the amount of fluid administered during the initial 24 h. In a retrospective study, a greater amount of fluid was not associated with a more favorable prognosis. A recent retrospective study reported that those patients who received <33 percent of their cumulative 72-h intravenous fluid volume during the initial 24 h of presentation were at risk for greater mortality. Thus, although aggressive fluid therapy during the first days of hospitalization is recommended by most guidelines and reviews on acute pancreatitis (AP), this recommendation is not supported by any direct evidence. It was aimed to evaluate the association between the amount of fluid administered during the initial 24 h of hospitalization and the incidence of organ failure (OF), local complications, and mortality in a prospective cohort study. It was included consecutive adult patients admitted with AP. Local complications and OF were defined according to the Atlanta Classification. Persistent OF was defined as OF of >48 h duration. Patients were divided into three groups according to the amount of fluid administered during the initial 24 h: group A: <3.1 L (less than the first quartile), group B: 3.1-4.1 L (between the first and third quartiles), and group C: >4.1 L (more than the third quartile). A total of 247 patients were analyzed. Overall, 32 patients (13 %) developed pancreatic necrosis, 14 (6 %) developed persistent OF, and 6 (2.4 %) patients died, 4 of them during the first 2 weeks due to sterile multiple OF and 2 of them later due to presumed infection of pancreatic necrosis (1 patient was inoperable due to comorbidity and it was decided not to perform fine needle aspiration (FNA) and the other patient had a negative FNA culture, but there was a high clinical suspicion of necrosis infection in both cases). Receiving >4.1 L fluid volume during the initial 24 h (group C), SIRS criteria at admission, and previous hemodialysis were associated with the development of persistent OF. The association was independent for group C and SIRS criteria in the multivariate analysis. Patients in group C, patients with body mass index >30, and patients with SIRS criteria had a significantly higher respiratory failure rate. The associations for group C and for the presence of SIRS criteria were maintained in the multivariate analysis. Patients who developed respiratory insufficiency (n=15) did not have a previous history of congestive heart failure or lung disease, except for one patient with obstructive sleep apnea syndrome without cor pulmonale. Patients who developed respiratory insufficiency or who were intubated received significantly more fluid volume during the initial 24 h. Patients in group C and those patients with an admission BUN >25 mg/dL had a higher incidence of renal failure. Statistical significance was maintained for group C in the multivariate analysis. Alcoholic etiology, hematocrit >44 percent, and SIRS criteria were significantly associated with the development of pancreatic necrosis. Hematocrit >44 percent and SIRS criteria were independently associated with necrosis in the multivariate analysis. Age >60 was a protective factor for pancreatic necrosis in both the bivariate and the multivariate analyses. Patients in group C, patients with alcoholic etiology, patients with hematocrit >44 percent, and those patients who met the criteria for SIRS developed acute collections more frequently. Statistical significance for group C, hematocrit >44 percent, and SIRS criteria were maintained in the multivariate analysis. Thus, in this study, patients below the first quartile (group A) did not have a poorer outcome than did patients between the first and the third quartiles (group B). Some experimental studies have suggested that impairment of the pancreatic microcirculation is a major contributor to the development of necrotizing pancreatitis. Therefore, it stands to reason that a great amount of fluid may prevent the development of this complication. However, a higher incidence of pancreatic necrosis in those patients who received ≤ 3.1 L during the initial 24 h was not reported. These preliminary data may suggest that a great amount of fluid does not prevent

necrosis; therefore, the development of pancreatic necrosis may be an early phenomenon and initial fluid therapy can hardly impair it. Given that this is an observational study, this possibility should be considered only as a hypothesis. The findings suggest the existence of a group of patients with an excellent prognosis: those patients who received a moderate amount of fluid (group B: 3-4 L within the first 24 h). This Goldilocks zone included patients without fluid sequestration, patients who did not need fluid overload because of the absence of hemoconcentration, shock, or renal failure (in cosmology, a “Goldilocks zone” is a region of space suitable for the evolution of life on a planet or planets that are not too close to – and not too far from – the local star). Patients who received >4 L of fluid had a higher incidence of collections. This may be caused by an early third-space fluid sequestration due to local complications. Fluid sequestration causes hemoconcentration, oliguria, and hypotension, causing the patient to require greater fluid volume to achieve stabilization. The hemoconcentration is likely to be a marker of pancreatic necrosis (early sequestration of fluid due to established necrosis) and may not precede it. In the study, only 1 of 15 patients who developed respiratory insufficiency did not have acute collections. Development of an abdominal compartment syndrome may induce the appearance of respiratory problems, and it has been suggested that a great amount of fluid may contribute to this process [113].

Early aggressive hydration

Early aggressive intravenous hydration is believed to prevent morbidity and mortality by preventing intravascular volume depletion and maintaining perfusion of the pancreas possibly preventing pancreatic necrosis. One study was initiated to determine the relationship between the observed decrease in mortality and the role of early aggressive hydration. A consecutive series of patients with acute pancreatitis from a single community hospital in 1998 were compared to a consecutive series of patients with acute pancreatitis from the same institution in 2008. Significantly more patients developed pancreatic necrosis; 26 (15 %) of 173 patients in 1998 compared to 4 (4 %) of 113 patients in 2008. The mean rate of hydration was significantly higher in 2008 compared with that in 1998. In 1998, hydration was provided at 184 mL/h during the first 6 hours and 188 mL/h during the first 12 hours compared with 284 mL/h during the first 6 hours and 221 mL/h during the first 12 hours in 2008. There was a significant decrease in mortality in 2008 compared with that in 1998 (3.5 % vs 12 %). It was concluded that the decrease in mortality seen in patients with acute pancreatitis during the last decade may be related to the increased aggressive hydration preventing pancreatic necrosis [114].

Enteral nutrition

To determine nutritional therapy practices of patients with severe acute pancreatitis (defined as those receiving critical care management in an intensive care unit or high-dependency unit) in Australia and New Zealand with focus on the choice of enteral nutrition or parenteral nutrition a prospective observational multicentered study was performed at 40 sites in Australia and New Zealand over 6 months. Included were those with severe acute pancreatitis diagnosed by elevated lipase and/or amylase. Patients with chronic pancreatitis were excluded. The primary outcome was the proportion of patients who received enteral nutrition, parenteral nutrition, or concurrent enteral nutrition/parenteral nutrition. Secondary outcomes included other aspects of nutritional therapy and the severity and clinical outcomes of acute pancreatitis. It was enrolled 121 patients and 117 were analyzed. The mean age was 61 years and 53 percent were men. Enteral nutrition was delivered to 58 percent and parenteral nutrition to 49 percent patients. Parenteral nutrition was more frequently used as the initial therapy (58 %) than enteral nutrition (42 %). The most common reason for parenteral nutrition prescription was the treating doctor's preference (60 %). Enteral nutrition (74 %) was more often used than parenteral nutrition (40 %) on any individual study day.

Concurrent enteral nutrition and parenteral nutrition occurred in 28 (24 %) patients on 14 percent of days. Complications of acute pancreatitis requiring critical care unit management were observed in 45 (39 %) patients. The median (interquartile range) duration of intensive care unit and hospital stay were 5 (2-10) and 19 (9-31) days, respectively. The hospital mortality rate was 15 percent, and there was a tendency toward higher mortality for patients who only received parenteral nutrition than for those who only received enteral nutrition (28 % vs 7 %). For patients with acute pancreatitis requiring critical care unit management in Australian and New Zealand intensive care units, enteral nutrition is used most commonly, but parenteral nutrition is more often used as the initial route of nutritional therapy. Given that clinical practice guidelines currently recommend enteral nutrition as the initial route of nutritional therapy in severe acute pancreatitis, improved education about and dissemination of these guidelines seems warranted [115].

Antibiotics

Early reports suggested prophylactic antibiotics given in severe pancreatitis prevent infection and death. More recent clinical trials do not support this benefit, and meta-analyses on the topic offer conflicting recommendations. Recognizing the increased mortality associated with infection of necrotic pancreatic tissue, antiinfective treatments have been applied, studied, and debated for over a decade. Some authors examined outcomes when antibiotics were given to all acute pancreatitis patients, while others looked specifically at populations where necrosis had occurred. Subsets undergoing ERCP procedures or taking probiotic formulations have also been studied. Randomized trials examining the effect of antibiotics on morbidity and mortality in acute pancreatitis began to appear in the 1970s. These early trials included patients with mild pancreatitis and used ampicillin as the treatment arm, showing no significant effect on mortality. In 1998, Golub et al published a meta-analysis of the first eight clinical trials to study this topic, including the three early trials mentioned above, and reported a mortality benefit not with ampicillin, but with the use of broad spectrum antibiotics expected to penetrate pancreatic tissue. Their meta-analysis included 514 total patients, and they noted that only one of the eight individual trials was able to show benefit with antibiotic therapy. Since this early effort, many systematic reviews have been written on this topic in an attempt to answer the important quandary of whether antibiotics can prevent infection and death in acute necrotizing pancreatitis. Note that despite inclusion of many of the same individual clinical trials, the meta-analyses draw differing conclusions regarding whether prophylactic antibiotics significantly reduce infection of necrotic pancreatic tissue or overall mortality among patients with ANP. Following initial efforts of Golub et al., Sharma et al published a 2001 meta-analysis rejecting for inclusion most of the earlier clinical trials. As with all later meta-analysis authors, they rejected trials using ampicillin for reasons of poor pancreatic penetrance and emerging bacterial resistance. In addition, they followed an important rule of meta-analysis in formulating a focused clinical question: whether prophylactic antibiotics improve outcomes in acute necrotic pancreatitis rather than in all acute pancreatitis. Including only trials that verified necrosis in their subjects, they further rejected Luiten et al and Delcenserie et al. This left 160 patients from three trials, and provided an overall conclusion that antibiotics significantly reduce mortality with a nonsignificant trend toward reduction in infection of necrotic pancreatic tissue. 2006 produced an explosion of meta-analysis effort with four publications reaching contradictory results. Heinrich et al and Villatoro et al both report mortality benefit but no reduction in infection of pancreatic necrosis with prophylactic antibiotics. Mazaki et al and Xiong et al report no significant benefit in either outcome. All four reviews agree on inclusion of trials by Nordback et al and Isenmann et al. In 2007, Dambrauskas et al included multiple trials that had been rejected by others for the following reasons. Also in 2007, de Vries et al was published late enough to include the second double-blinded study on this topic, a multicenter trial by Dellinger et al comparing meropenem with placebo and finding no difference in infected

necrosis or mortality. Over time, more individual trials allowed larger meta-analyses, and a third higher quality, double-blind trial showed no significant difference with prophylactic antibiotics. Luckily, we now have three RCTs that are of higher quality, including a placebo group and keeping the patients with ANP and their clinicians blind to group allocation. Blinding reduces bias in outcome reporting, particularly for inadvertent partiality regarding which patients are sent for cultures of necrosed pancreatic tissue. Two of these trials are also stronger because they are multicenter studies. All three of these trials reported no difference in rates of pancreas infection or mortality, providing the clearest answer that prophylactic antibiotics should not be part of clinical protocols for treatment of severe acute pancreatitis today. It is difficult to imagine a topic that investigators have tried harder to solve than one which has generated 14 meta-analyses in just under as many years. The cumulative data now conclude that prophylactic antibiotics are not beneficial, and might be harmful, in patients whose acute pancreatitis has evolved to necrosis of the pancreas [066].

Intravenous local anesthetics

Intravenous local anesthetics may ameliorate pain and clinical course in patients with major abdominal surgery. To investigate their effects in acute pancreatitis 46 consecutive patients with acute pancreatitis randomly received intravenous procaine (2 g/24 h) or placebo for 72 hours in a double-blind fashion. Pain severity (visual analog scale, 0-100), on-demand pain medication (metamizole and/or buprenorphine), and the clinical course were monitored every 24 hours. Data of 44 patients were subjected to intention-to-treat analysis. Although there were no differences between groups before treatment, procaine treatment was associated with a stronger decrease in pain compared with placebo (median visual analog scale decrement, -62 vs -39). Moreover, there was a greater proportion of patients with adequate ($\geq 67\%$) pain reduction (75 % vs 43 %), less use of additional analgesics, and overall analgesic superiority. Compared with placebo, the proportion of patients hospitalized after 2 weeks was reduced by 80 percent after procaine treatment. It was concluded that these findings support the hypothesis that systemic administration of local anesthetics might improve pain and accelerate clinical recovery in acute pancreatitis [116].

Melatonin

Melatonin plays a protective role in experimental acute pancreatitis (AP) because of its antioxidative, antiinflammatory, and immunomodulatory effects. One study presented the first data on the dynamic changes of endogenous melatonin in the early phase of human AP. Morning (08:00 hr) serum melatonin concentrations were measured by ELISA in 75 patients with AP for the first 5 days after the onset of pain. According to the Atlanta classification, 26 patients suffered a mild AP (MAP). The other 49 developed a severe AP (SAP). Median melatonin concentrations of healthy volunteers were used as a control. Median melatonin level in healthy controls was 19 pg/mL. Levels of melatonin were significantly higher in the first 24 hr after onset of disease in patients with MAP compared to those with SAP, 51 versus 9 pg/mL. Melatonin values were the same in MAP and SAP during the remainder of the study period. Melatonin concentrations during the first 24 hr after the onset of pain in younger patients (<35 yrs old) were significantly higher than levels in older patients (>35 yrs): 73 versus 9 pg/mL. No correlation existed between melatonin levels and the following parameters: gender, etiology (biliary versus alcohol induced), and histological findings (edematous versus necrotizing versus infected necrosis). High endogenous melatonin serum levels in the first 24 hr after the onset of AP played a protective role and favoured a mild course of the disease in humans, especially in young patients [117].

Resveratrol

Acute pancreatitis is a common kind of acute abdominal disease. The management of severe acute pancreatitis (SAP) is a challenge because of its high morbidity, which is due to systemic inflammatory response syndrome and multiorgan dysfunction syndrome. Therefore, it is important to explore therapies to control the disease's progression. A series of in vivo and in vitro experiments has demonstrated that resveratrol-an extract from Chinese herbs, grapes, and many plants-exhibits a wide range of biological and pharmacological activities, including anti-inflammatory, antioxidation, and chemopreventive effects, as well as the inhibition of platelet aggregation, which could benefit the treatment of SAP. Here, it was examine the possible mechanism of resveratrol in treating the progression of SAP. Resveratrol could inhibit the production and progression of SAP through down-regulating pro-inflammatory cytokines, improving microcirculation, modulating cell apoptosis, and blocking calcium overload. It was proposed that resveratrol has a potentially therapeutic effect on the progression of severe acute pancreatitis [118].

Abdominal compartment syndrome

Once considered mostly a postsurgical condition, intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS) are now thought to increase morbidity and mortality in many patients receiving medical or surgical intensive care. Animal data and human observational studies indicate that oliguria and acute kidney injury are early and frequent consequences of IAH/ACS and can be present at relatively low levels of intra-abdominal pressure (IAP). Among medical patients at particular risk are those with septic shock and severe acute pancreatitis, but the adverse effects of IAH may also be seen in cardiorenal and hepatorenal syndromes. Factors predisposing to IAH/ACS include sepsis, large volume fluid resuscitation, polytransfusion, mechanical ventilation with high intrathoracic pressure, and acidosis, among others. Transduction of bladder pressure is the gold standard for measuring intra-abdominal pressure, and several nonsurgical methods can help reduce IAP. The role of renal replacement therapy for volume management is not well defined but may be beneficial in some cases. IAH/ACS is an important possible cause of acute renal failure in critically ill patients and screening may benefit those at increased risk [119].

Increased intra-abdominal pressure (IAP), also referred to as intra-abdominal hypertension (IAH), affects organ function in critically ill patients and may lead to abdominal compartment syndrome (ACS). Although initially described in surgical patients, IAH and ACS also occur in medical patients without abdominal conditions. IAP can be measured easily and reliably in patients through the bladder using simple tools. The effects of increased IAP are multiple, but the kidney is especially vulnerable to increased IAP because of its anatomic position. Although the means by which kidney function is impaired in patients with ACS is incompletely elucidated, available evidence suggests that the most important factor involves alterations in renal blood flow. IAH should be considered as a potential cause of acute kidney injury in critically ill patients; its role in other conditions, such as hepatorenal syndrome, remains to be elucidated. Because several treatment options (both medical and surgical) are available, IAH and ACS should no longer be considered irrelevant epiphenomena of severe illness or critical care. An integrated approach targeting IAH may improve outcomes and decrease hospital costs, and IAP monitoring is a first step toward dedicated IAH management. IAH prevention, most importantly during abdominal surgery but also during fluid resuscitation, may avoid ACS altogether. However, when ACS occurs and medical treatment fails, decompressive laparotomy is the only option [120].

Pancreatic necrosis

The classic treatment of infected pancreatic necrosis (IPN) is surgical debridement and drainage. This study reviews our experience with nonoperative percutaneous catheter drainage and serial lavage as primary treatment in patients with IPN. Between 1993 and 2009, a prospective nonselected series of 63 consecutive patients with microbiologically confirmed IPN were enrolled with the intent of treating them nonoperatively, and they were retrospectively analyzed. Catheters were placed percutaneously in the interventional radiology (IR) suite, and were used to lavage and debride the necrosis 1-3 times per week. The lavages continued on an outpatient basis by IR, and the catheters were removed with disease resolution. One patient rapidly became unstable and had to be taken primarily for open debridement. In the remaining 62 patients, 57 survived, for an overall mortality rate of 8 percent. Fifty patients were treated solely with percutaneous lavage, and 47 survived. Mean hospital length of stay was 61 days, ranging from 6 to 190 days. Mean length of outpatient treatment was 42 days, ranging from 3 to 180 days. Mean number of lavages was 21, ranging from 11 to 75. Eleven patients (18 %) deteriorated during percutaneous treatment and required laparotomy, and 9 of these survived. One patient treated percutaneously resolved his sepsis but had a persistent pancreatic fistula and was managed with pancreaticojejunostomy. It was concluded that percutaneous catheter drainage and serial lavage are an effective alternative to open surgical debridement in patients with IPN. Overall survival is excellent, and most patients avoid the morbidity of open debridement. A minority of patients deteriorates, but most of those can be salvaged with open drainage [121].

Treatment of patients with necrotizing pancreatitis has become more conservative and less invasive, but there are few data from prospective studies to support the efficacy of this change. It was performed a prospective multicenter study of treatment outcomes among patients with necrotizing pancreatitis. It was collected data from 639 consecutive patients with necrotizing pancreatitis, from 2004 to 2008, treated at 21 Dutch hospitals. Data were analyzed for disease severity, interventions (radiologic, endoscopic, surgical), and outcome. Overall mortality was 15 percent (n=93). Organ failure occurred in 240 patients (38 %), with 35 percent mortality. Treatment was conservative in 397 patients (62 %), with 7 percent mortality. An intervention was performed in 242 patients (38 %), with 27 percent mortality; this included early emergency laparotomy in 32 patients (5 %), with 78 percent mortality. Patients with longer times between admission and intervention had lower mortality: 0 to 14 days, 56 percent; 14 to 29 days, 26 percent; and >29 days, 15 percent, which was a significant difference. A total of 208 patients (33 %) received interventions for infected necrosis, with 19 percent mortality. Catheter drainage was most often performed as the first intervention (63 % of cases), without additional necrosectomy in 35 percent of patients. Primary catheter drainage had significantly fewer complications than primary necrosectomy (42 % vs 64 %). Patients with pancreatic parenchymal necrosis (n=324), compared with patients with only peripancreatic necrosis (n=315), had a higher risk of organ failure (50 % vs 24 %) and mortality (20 % vs 9 %) It was concluded that approximately 62 percent of patients with necrotizing pancreatitis can be treated without an intervention and with low mortality. In patients with infected necrosis, delayed intervention and catheter drainage as first treatment improves outcome [122].

Percutaneous drainage

The role of percutaneous catheter drainage (PCD) in patients with (infected) necrotizing pancreatitis was evaluated. A systematic literature search was performed. Inclusion criteria were: consecutive cohort of patients with necrotizing pancreatitis undergoing PCD as primary treatment for peripancreatic collections; indication for PCD either (suspected) infected necrosis or symptomatic sterile pancreatic necrosis; and outcomes reported to include percentage of infected peripancreatic collections, need for additional surgical necrosectomy,

complications and deaths. Exclusion criteria were: cohort of fewer than five patients; cohort included patients with chronic pancreatitis; selected subgroup of patients with acute pancreatitis studied, such as those with pseudocysts, pancreatic abscesses and/or exclusively sterile pancreatic necrosis; and cohort in which PCD was combined with another minimally invasive strategy and results for PCD alone not reported separately. Eleven studies, including 384 patients, fulfilled the inclusion criteria. Only one study was a randomized controlled trial; most others were retrospective case series. Four studies reported on the presence of organ failure before PCD; this occurred in 67 percent of 116 patients. Infected necrosis was proven in 271 (71 %) of 384 patients. No additional surgical necrosectomy was required after PCD in 214 (56 %) of 384 patients. Complications consisted mostly of internal and external pancreatic fistulas. The overall mortality rate was 17 percent (67 of 384 patients). Nine of 11 studies reported mortality separately for patients with infected necrosis undergoing PCD; the mortality rate in this group was 15 percent (27 of 175). It was concluded that a considerable number of patients can be treated with PCD without the need for surgical necrosectomy [123].

Minimally invasive retroperitoneal pancreatic necrosectomy

One article described a case series outlining the experience and results of the retroperitoneal minimally invasive pancreatic necrosectomy (MIPN) procedure performed by, or done under the supervision of, a single surgeon. All data of the patients who underwent MIPN from 2006 to 2008 were entered into a prospectively maintained, computerized database. A total of 93 MIPN procedures were performed on 32 patients. All patients had severe acute pancreatitis. The median number of MIPN procedures per patient was 3. Only 6 patients needed intensive care unit (ICU) admission after MIPN. There were 15 complications, which included bleeding requiring transfusion (n=3), bowel fistulae (n=7), thromboembolic events (n=2) and acute myocardial infarction (n=3). Four patients died after the procedure (13 %); 1 died of ongoing multiorgan failure in spite of the MIPN. Four patients developed pancreatic pseudocysts within the follow-up period of 2 years. Three of these patients required intervention. This case series demonstrates that MIPN can be performed with acceptable morbidity and mortality and with good end results. The ICU dependency after the procedure is minimal. As seen in this series, multiple MIPNs may be needed to eradicate the necrosis satisfactorily [124].

Postnecrotic fistulas

Endoscopic transpapillary stenting (ETS) of the pancreatic duct facilitates ductal outflow and may reduce time to pancreatic fistula closure. Pancreatic fistulas often occur after intervention in necrotizing pancreatitis and frequently close only after months of conservative treatment. From a prospective cohort of patients with acute pancreatitis admitted in 15 hospitals (2004-2007), all patients who underwent ETS or conservative treatment for a pancreatic fistula were identified. Safety, feasibility, and outcome of ETS were evaluated. Furthermore, a literature review was performed for similar studies in necrotizing pancreatitis. Of 731 patients with acute pancreatitis, 19 patients were treated with ETS and 16 patients were treated conservatively for a pancreatic fistula. Fistula closure was achieved in 16 of 19 patients (84 %) in the ETS group and in 8 of 12 patients (75 %) in the conservative group. The median time to fistula closure after ETS was 71 days (interquartile range, IQR, 34-142) compared with 120 days (IQR 51-175 days) in the conservative group. Complications were observed in 6 patients. A total of 10 studies reporting the results of 281 patients with stent placement for pancreatic fistulas were included in the literature review. Fistula closure was achieved in 200 patients (71 %). Stent-related complications were reported in 9 percent of patients. It was concluded that ETS seems a feasible and safe alternative to conservative

treatment in patients with pancreatic fistulas after intervention for necrotizing pancreatitis [125].

Post-pancreatitis colosplenic fistula

It was reported a case of spontaneous rupture of a splenic subcapsular hematoma into a colonic diverticulum presenting itself as a per rectum bleed. Splenic complications associated with pancreatitis, such as intrasplenic pseudocyst or splenic hematoma/rupture, are rare with an estimated incidence of 2 percent. Reports suggest that splenic complications in pancreatitis are associated with 1 of 3 things: distal pseudocysts, acute necrotizing pancreatitis, or splenic vein occlusion. The treatment for subcapsular hematoma of the spleen is not universally agreed, but it can resolve spontaneously. Splenic fistulation with the colon has been reported before in cancer patients. No reported cases describe the management of colosplenic fistulation on a background of pancreatitis [126].

Pleural effusion

Pancreaticopleural fistula is a condition in which pancreatic enzymes drain into the pleural cavity. It is a complication of pancreatic disease and usually presents with thoracic rather than abdominal symptoms. Although unusual, it should be included in the differential diagnosis to substantial and persistent unilateral pleural effusion. It was reported a case of a 71-year-old man who presented with dyspnoea. During two months, the patient underwent pulmonary evaluation before the pancreas was identified as the site of primary pathology. The key to the diagnosis was an elevated level of pleural fluid amylase [127].

Endocrine function postpancreatic

One study aimed to investigate the impairment of pancreatic endocrine function and the associated risk factors after acute pancreatitis (AP). Fifty-nine patients were subjected to tests of pancreatic function after an attack of pancreatitis. The mean time after the event was 3.5 years. Pancreatic endocrine function was evaluated by fasting blood glucose (FBG), glycosylated hemoglobin, fasting blood insulin, and C-peptide. Homeostasis model assessment was used to evaluate insulin resistance and islet beta-cell function. Pancreatic exocrine function was evaluated by fecal elastase 1. Factors that could influence endocrine function were also investigated. Nineteen patients (32 %) were found to have elevated FBG, whereas 5 (8 %) had abnormal glycosylated hemoglobin levels. The levels of FBG, fasting blood insulin, and C-peptide were significantly higher in patients than in controls. The islet beta-cell function of patients was significantly lower than that of controls, whereas insulin resistance index was higher among patients. Obesity, hyperlipidemia, and diabetes-related symptoms were found to be associated with endocrine insufficiency. Pancreatic exocrine functional impairment was found at the same time. Endocrine functional impairment with insulin resistance was found in patients after AP. Obesity, hyperlipidemia, and diabetes-related symptoms increased the likelihood of developing functional impairment after AP [128].

Acute pancreatitis in children

Acute pancreatitis is a reversible inflammatory process of the pancreas. Although the disease process may be limited to pancreatic tissue, it also can involve peripancreatic tissues or more distant organ sites. Acute pancreatitis is a disease with complex mechanisms. Polymorphisms in genes relating to pancreatic diseases play considerable

roles in conjunction with environmental factors in determining an individual's susceptibility to developing pancreatitis. The clinical presentation of pancreatitis is various in children and adolescents, ranging from intrauterine congenital onset with sequelae of early exocrine pancreatic insufficiency as in the diseases of cystic fibrosis and Shwachman-Diamond syndrome to postnatal onset as a consequence of embryologic anomalies affecting pancreatic drainage postulated to exist in pancreas divisum, or of traumatic, obstructive, hemodynamic, metabolic, or biochemical insults. The etiology is often elusive, with up to 30 percent of cases being idiopathic. Most common acute pancreatitis-related complications include pulmonary, renal, cardiovascular, and central nervous system dysfunctions. In literature, pleural effusion is reported as having an incidence, in the adult population affected by pancreatitis, of 3 to 17 percent, 3 times more frequent in the left hemithorax than in the right one. This type of manifestation seems to be even rarer in the pediatric population: in fact, most cases of pleural effusion secondary to pancreatitis are found in patients aged 20 to 55 years. It was now reported the case of a 7-year old boy with acute pancreatitis who had been presenting with moderate cough and yet a massive pleural effusion but without any other clinical symptoms. A primary cause of pancreatitis is frequently found in young children, with the most common causes being blunt trauma, drugs, viral infections, periampullary obstruction, systemic illnesses, and genetic predispositions. Pleural effusion alone is a rare manifestation of pancreatitis. This is true mainly in the pediatric population. The presence of pleural effusion is currently considered as an indication of severe pancreatitis and not just as a marker of the disease. Patients presenting with pleural effusions usually have a hemorrhagic drainage and laboratory findings characterized by high amylase, protein, and lactic acid dehydrogenase levels. Most of these effusions are left-sided, but sometimes radiographs show bilateral effusion or, rarely, right-sided ones. Symptomatic pleural effusions may often require thoracentesis. The pathophysiology of this complication of the pancreatic disorder may be represented by a transdiaphragmatic lymphatic blockage or by a pancreaticopleural fistulae secondary to leak and disruption of the pancreatic duct or pseudocyst caused by an episode of acute pancreatitis. Pancreatic enzymes can track up into the mediastinum and then rupture into the pleural cavity either on the left side or bilaterally and so create a connection between the pancreatic duct and the pleural cavity [129].

To assess specific etiologies of acute recurrent pancreatitis at a single Italian pediatric cystic fibrosis (CF) center it was studied, retrospectively, 78 young patients (39 female subjects; mean age at diagnosis, 9 ± 5 years) affected by acute recurrent episodes of pancreatitis, remained etiologically undiagnosed at first-level assessment. All patients were submitted to endoscopic retrograde cholangiopancreatography to exclude biliopancreatic malformations and tested for CF by a sweat chloride test. Most patients also were studied for the research of CFTR, PRSS1, and SPINK1 gene mutations. A high percentage of family history for chronic pancreatitis was observed (21 %). The sweat test identified 8 subjects (10 %) with classic CF (2 patients) or at risk for CF (6 patients). Genetic analysis showed mutations in CFTR, SPINK1, and PRSS1 genes in 40 percent, 7 percent, and 5 percent of patients, respectively. A biliopancreatic malformation was diagnosed in 15 patients (19 %). It was also observed biliary lithiasis (5 patients), congenital pancreatic polycystosis (2 patients), a case of dyslipidemia, and 1 patient with a posttransplantation, drug-induced pancreatitis [130].

Traditional Chinese medicine

The aim of one study was to observe the dynamic changes of immunity for patients with severe acute pancreatitis (SAP) and intervention by traditional Chinese medicine. Twenty-three patients who met the inclusion criteria were randomized to combined treatment of traditional Chinese medicine and Western medicine (TCM) or conventional western medicine treatment (WM) groups. The clinical data for all patients were collected. Peripheral venous

blood samples were obtained from patients on days 1, 7, 14, and 28 after admission. Biochemical data including the percentage of CD4+/CD8+/natural killer (NK) cells/B lymphocytes/HLA-DR and CD4+/CD8+ ratio in serum were determined by flow cytometer. Patients' characteristics and immunity at admission were similar between the two groups. The secondary infection was different. The levels of T-lymphocyte subsets in the TCM group were quite different from the WM group, with much more the percentage of CD4+ and the CD4+/CD8+ ratio on days 7, 14, and 28 and much less the percentage of CD8+ on days 4 and 28. On days 14 and 28, the levels of NK cells and B lymphocytes were significantly higher in the TCM group compared with the controls. Compared with the TCM group, the levels of HLA-DR were significantly decreased in the WM group on days 7, 14, and 28. The immune dysregulation exists in the development and progression of SAP. The combined treatment of traditional Chinese medicine and western medicine can upregulate the patient's immune and maintain the immune balance [131].

Case reports

HELLP syndrome

Pancreatic panniculitis represents a rare cutaneous disorder most commonly associated with acute or chronic pancreatitis or pancreatic carcinoma. It was described a case of a 17-year-old woman who presented with a 2-day history of erythematous patches involving her bilateral knees and tender, scattered red-brown nodules involving her bilateral anterior shins. She was seen during a hospitalization for emergent cesarean section and her hospital course was complicated by HELLP syndrome (defined by the presence of hemolysis, elevated liver enzymes, low platelet count), acute fatty liver of pregnancy and pancreatitis. The characteristic histopathologic findings, including ghost cells, fat necrosis and granular basophilic material with dystrophic calcification, appear in later lesions. In early lesions, as was shown in this case, a neutrophilic subcutaneous infiltrate raises a differential diagnosis including infection, subcutaneous Sweet's syndrome or atypical erythema nodosum. Early recognition is critical, as skin lesions may precede the development of pancreatitis. The effects of pancreatitis may be life threatening [132].

CHRONIC PANCREATITIS

Overview

Chronic pancreatitis is a progressive fibroinflammatory disease that exists in large-duct (often with intraductal calculi) or small-duct form. In many patients this disease results from a complex mix of environmental (e.g. alcohol, cigarettes, and occupational chemicals) and genetic factors (e.g. mutation in a trypsin-controlling gene or the cystic fibrosis transmembrane conductance regulator); a few patients have hereditary or autoimmune disease. Pain in the form of recurrent attacks of pancreatitis (representing paralysis of apical exocytosis in acinar cells) or constant and disabling pain is usually the main symptom. Management of the pain is mainly empirical, involving potent analgesics, duct drainage by endoscopic or surgical means, and partial or total pancreatectomy. However, steroids rapidly reduce symptoms in patients with autoimmune pancreatitis, and micronutrient therapy to correct electrophilic stress is emerging as a promising treatment in the other patients. Steatorrhoea, diabetes, local complications, and psychosocial issues associated with the disease are additional therapeutic challenges [133].

The disease is uncommon in Europe and the USA; its prevalence in France is for example 26 per 100 000 people. This prevalence is considerably lower than the figure of 114-200 per 100 000 in south India [133].

Traditionally, chronic pancreatitis has been classed as fundamentally different from acute pancreatitis – the latter is usually characterised by restoration of normal pancreatic histology after full clinical recovery. However, acute, recurrent acute, and chronic pancreatitis are now regarded as a disease continuum. There is an overlap in causative factors, both genetic and environmental; experimental protocols can be modified to induce each condition, and the pancreatitis attack is stereotyped: patients have severe abdominal pain and increased blood amylase, lipase, and trypsinogen. In humans, the main symptom of chronic pancreatitis is usually pain, which occurs as attacks that mimic acute pancreatitis or as constant and disabling pain [134].

In patients who develop large-duct chronic pancreatitis, studies in the quiescent phase of the disease show that the composition of pancreatic fluid changes in a manner that, for uncertain reasons, facilitates protein deposits; the precursors to calcium carbonate stones. There is an early increase in secretion of enzyme and calcium, but a decrease in the serine protease inhibitor Kazal type 1 (SPINK 1), bicarbonate, and citrate. Lactoferrin and mucin are increased in pancreatic juice. Concentrations are also altered of two secretory stress protein pancreatitis associated protein (PAP), and variable concentration of pancreatic stone protein (PSP), formerly called lithostatin, that tend to form fibrous lattices upon partial digestion by trypsin. On histology, the defining triad of stable disease (irrespective of main causes or location) is acinar loss, mononuclear cell infiltration, and fibrosis. The early lesions are distributed in patches; thus, normal findings on needle biopsy are unreliable. Each inflammatory attack can cause foci of fat necrosis that seem to lead to both pseudocysts and fibrosis. Acinar cells, which are hyperplastic at disease outset, show strong expression of cytochrome P450 (CYP) monooxygenases, as do proliferated islets of Langerhans. Fibrosis is a sign that interstitial stellate cells are activated in chronic pancreatitis; these cells play a central part in disease progression by regulating the synthesis and degradation of extracellular matrix proteins [133].

In adults, excluding those with cystic fibrosis, 90-95 percent of patients are regarded as having alcoholic or idiopathic disease. Alcohol has long been regarded as the leading cause of chronic pancreatitis in Europe, the USA, Brazil, Mexico, and South Africa, and is now regarded as the main cause of the disease also in Australia and South Korea. Experimental studies have shown that, although the pancreas processes ethanol efficiently (via a non-oxidative route that produces fatty acid ethyl esters, and by oxidation via the acetaldehyde pathway), its metabolites injure acinar cells and activate stellate cells in vitro. Hence, the finding of a latent interval of 15 years or more in patients who consumed 150 g or more of ethanol per day is unsurprising. Moreover, less than 10 percent of people who drink alcohol in excess develop the disease. Collectively, findings suggest that other factors interact to amplify ethanol toxicity in vivo [133].

Alcoholic chronic pancreatitis presents in the fourth or fifth decade of life and mainly affects men. Idiopathic disease has early-onset (second decade) and late-onset (sixth decade) forms, which have equal gender distribution. Presenting features of chronic pancreatitis usually fall into one of four groups: apparent acute or recurrent acute pancreatitis (the true diagnosis of chronic pancreatitis is suspected when attacks recur after cholecystectomy); constant pain; symptoms and signs of local complications of the disease (e.g. pseudocyst, obstruction of adjacent organs, or vascular thrombosis); or complaints that suggest exocrine or endocrine pancreatic failure, or both, by which stage pancreatic calculi are often present. In alcoholic disease, the interval from first attack to steatorrhea (signifying >95% loss of acini) is around 13 years, which is substantially shorter than in early-onset idiopathic disease or hereditary pancreatitis (≥ 26 years). Pancreatic calculi appear earliest in tropical

pancreatitis, and earlier in alcoholic than idiopathic disease. Diabetes might precede, begin at the same time as, or start after steatorrhea. Pain is the over-riding symptom in all but 10-15 percent of cases of chronic pancreatitis; these cases are usually elderly patients with idiopathic disease. The pain is wearying and occurs in episodes that last about 1 week, or is constant. It starts in the epigastrium and moves through to the dorsal spine or localises to the left hypochondrium, radiating to the left infrascapular region. The pain is sometimes associated with nausea and vomiting and can be partially eased by sitting up and leaning forward or by application of local heat or other counterirritants to the dorsal spine or epigastrium. The pain can be so severe that patients fear food and lose weight. Patients should be advised to avoid alcohol and cigarettes, although there is no evidence that abstinence from alcohol slows the disease and the effect of alcohol on pain is debated [133].

Excessive alcohol use is associated with a variety of negative health outcomes, including liver disease, upper gastrointestinal bleeding, and pancreatitis. To determine the 2-year risk of gastrointestinal-related hospitalization and new-onset gastrointestinal illness based on alcohol screening scores male (n=215,924) and female (n=9,168) outpatients who returned mailed questionnaires and were followed for 24 months. Alcohol Use Disorder Identification Test-Consumption Questionnaire (AUDIT-C), a validated three-item alcohol screening questionnaire (0-12 points) was used. Two-year risk of hospitalization with a gastrointestinal disorder was increased in men with AUDIT-C scores of 5-8 and 9-12 (OR 1.54), and women with AUDIT-C scores of 9-12 (OR 6.84). Men with AUDIT-C scores of 5-8 and 9-12 had increased risk of new-onset liver disease (OR 1.49), and new-onset of upper gastrointestinal bleeding (OR 1.28). Two-year risk of new-onset pancreatitis in men with AUDIT-C scores 9-12 was also increased (OR 2.14). Excessive alcohol use as determined by AUDIT-C is associated with 2-year increased risk of gastrointestinal-related hospitalization in men and women and new-onset liver disease, upper gastrointestinal bleeding, and pancreatitis in men. These results provide risk information that clinicians can use in evidence-based conversations with patients about their alcohol consumption [135].

Ordinary chronic pancreatitis has a high mortality rate – nearly 50 percent within 20-25 years of disease onset, as a result of complications of an attack, coexisting disease, or the effects of alcoholism. Patients with chronic pancreatitis have an increased risk of pancreatic cancer. Although the risk of pancreatic cancer is especially high in patients with hereditary pancreatitis, they do not have a higher mortality risk than the general population. Autoimmune pancreatitis also does not affect long-term survival [133].

The incidence of chronic pancreatitis grows slowly but steadily. At present, alcohol is the most frequent risk factor, although the new forms of so called non-alcoholic chronic pancreatitis, such as genetically induced pancreatitis and its autoimmune variety, are carefully watched. Alcohol consumption continues to be most closely associated with the disease, though it is no more than a risk factor and other aspects, e.g. genetic predisposition, are prerequisite to the disease development. Imaging methods play a fundamental role in diagnosing the disease; non-invasive magnetic resonance and CT, invasive but safe endosonography, and diagnostically rarely used ECRP that, because of its invasive nature, is currently predominantly used for therapeutic purposes. Genetic markers are also exploited, including CFTR mutation, SPINK 1 and PRSS 1 gene, immunoglobulin G4 in the autoimmune form of the disease as well as, alternatively, pancreatic biopsy. Disease symptoms, i.e., pancreatic malabsorption (enzymes with high lipase content) and pancreatic pain are treated conservatively, with paracetamol as the first line therapy for pain followed, if necessary, by so called synaptic analgesics. Alternatively, endoscopic techniques (drainage) or surgery (drainage and resection) are applied. Hereditary and non-hereditary chronic pancreatitis is among the risk factors for pancreatic cancer and thus patients with these diseases should be closely followed up [136].

Personalized medicine

Personalized medicine integrates an individual's genetic and other information for the prevention or treatment of complex disorders, and translational research seeks to identify those data most important to disease processes based on observations at the bench and the bedside. To understand complex disorders such as chronic pancreatitis, inflammatory bowel disease, liver cirrhosis, and other idiopathic chronic inflammatory diseases, physician-scientists must systematically collect data on relevant risks, clinical status, biomarkers, and outcomes. The author describes a "matrix academic division" (MAD), a highly effective academic program created at the University of Pittsburgh School of Medicine and the University of Pittsburgh Medical Center using translational research to rapidly develop personalized medicine for digestive diseases. MAD is designed to capture patient-specific data and biologic samples for analysis of steps in a complex process (reverse engineering), reconstructing the system conceptually and mathematically (disease modeling), and deciphering disease mechanism in individual patients to predict the effects of interventions (personalized medicine). MAD draws on the expertise of the medical school's and medical center's physician-scientists to translate essential disease information between the bed and the bench and to communicate with researchers from multiple domains, including epidemiology, genetics, cell biology, immunology, regenerative medicine, neuroscience, and oncology. The author illustrates this approach by describing its successful application to the reverse engineering of chronic pancreatitis [137].

Incidence

Population-based estimates for chronic pancreatitis (CP) are scarce. It was determined incident CP hospitalization rates and the risk of pancreatitis-related readmissions in Allegheny County, Pennsylvania, USA. It was used Pennsylvania Health Care Cost Containment Council (PHC4) dataset to identify all unique White and Black Allegheny County residents with incident hospitalization for CP from years 1996–2005. It was noted presence of alcoholism codes (from one year before index hospitalization until last contact) and pancreatitis-related readmissions until the third quarter of 2007. Age-, gender-, and race-adjusted (to US 2000 population) rates/100,000 were calculated. 988 unique County residents with incident hospitalization for CP were identified. Of these, 38 percent also received alcoholism codes. Overall hospitalization rate was 7.75/100,000 (95 % confidence interval 7.26 to 8.24), which remained stable throughout the study period. Patients with alcoholism codes were significantly younger (47 vs 58 years), more likely to be male (71 vs 37 %), and black (39 vs 18 %). Hospitalization rates were significantly higher (2.4-fold) in blacks (vs whites), particularly for those with alcoholism codes. During follow-up (median 45 months), pancreatitis-related readmissions were common, significantly more so for patients with alcoholism codes. It was concluded that CP hospitalization rates over a one-decade period were stable. Readmissions were highest among patients with a diagnosis of alcoholism [138].

Epidemiology

It was asked why so few working-class Africans of Soweto have chronic pancreatitis (CP) when alcoholism is the norm. Twenty-one alcoholics with acute psychosis but normal pancreas were investigated for lifestyle, micronutrient status, electrophilic stress, and iron overload. Alcoholics consumed more ethanol daily than did 14 previously studied patients with CP; cigarette usage was similar; both groups had even poorer vitamin C status than 14 healthy controls, and no participant had iron overload. The CP group had higher scores for exposure to occupational xenobiotics than did alcoholics, with lower plasma glutathione and

urinary inorganic sulfate. Further analysis identified hyperhomocysteinemia in the alcoholic set, with lower vitamin B12, higher folic acid, and similar vitamin B6 levels compared with controls. It was concluded that the transition from alcoholism to CP in Soweto is associated with occupational exposure to xenobiotics. Among detoxification systems that are strained thereby, glutathione and inorganic sulfate depend on methionine intake, which is ample in Sowetans, whereas vitamin C, which exerts a glutathione-sparing effect, is deficient. Hence, a daily tablet of vitamin C may enable community prophylaxis against the disease-but homocysteine status would need monitoring [139].

Diagnostics

To assess the feasibility of visualizing noninvasively the physiologic flow of pancreatic juice by using serial magnetic resonance cholangiopancreatography (MRCP) with a spatially selective inversion-recovery (IR) pulse in volunteers and patients with pancreatic disease. On study included 20 healthy volunteers and three patients with acute pancreatitis. MRCP with a spatially selective IR pulse was repeatedly performed every 15 seconds during a total of 10 minutes (total of 40 images). MRCP images were evaluated for the presence, frequency, and magnitude of pancreatic juice inflow within the tagged area. The two groups were compared by using the Mann-Whitney test. Pancreatic juice inflow was observed in all healthy volunteers and in two of three patients with acute pancreatitis. The pancreatic fluid inflow was observed 25-37 times (median, 32 times; mean, 31 times; range, 25-37 times) in a series of 40 images in 12 healthy volunteers, while it was seen 0-11 times (median, 2 times; mean, 4.3 times; range, 0-11 times) in a series of 40 images in the three patients with acute pancreatitis. No regularity in the timing of the pancreatic fluid inflow was noted. The distance that the pancreatic fluid moved in the pancreatic duct within the tagged area was significantly longer in healthy volunteers (median grade, 2.5) than in patients with acute pancreatitis. It was concluded that the physiologic flow of the pancreatic juice can be visualized noninvasively with serial MRCP by using a spatially selective IR pulse [140].

EUS

The Rosemont criteria (RC) were recently proposed by expert consensus to standardize endoscopic ultrasound (EUS) features and thresholds for diagnosing chronic pancreatitis (CP); however, they are cumbersome and are not validated. To determine interobserver agreement between RC and conventional criteria (CC), and to assess intertest agreement in the diagnosis of CP 36 consecutive patients who underwent EUS for abdominal pain or pancreatitis were retrospectively reviewed. Anonymized images were independently chosen as best representations of the pancreatic body and reviewed by three experts who recorded the presence of CC and RC features. Agreement (proportion and kappa statistic) between CC and RC was calculated. Interobserver agreement within the CC and RC was assessed. Secondary comparisons with endoscopic retrograde cholangiopancreatography were made where available. Using CC, 60 readings (83 %) were negative for CP, while 12 readings were positive. Using RC, 59 readings (82 %) were negative for CP, while 13 were positive. The weighted kappa for interobserver agreement for CC (four categories: normal/low probability, indeterminate, high probability or calcific) was 0.50, with 80 percent overall agreement, versus 0.27 and 68 percent for the four RC categories (normal, indeterminate, suggestive of and consistent with). Agreement on a positive diagnosis with CC was 86 percent; for RC, agreement was lower at 81 percent. For patients who underwent endoscopic retrograde cholangiopancreatography (n=12), false-negative and false-positive rates between CC and RC did not appear to be different. It was concluded that the Rosemont criteria do not appear to achieve the goals of improving accuracy and interobserver agreement for diagnosing chronic pancreatitis [134].

Alcohol-induced chronic pancreatitis

One paper summarized the relationships between different patterns of alcohol consumption and various non-communicable disease (NCD) outcomes and estimates the percentage of NCD burden that is attributable to alcohol. A narrative review, based on published meta-analyses of alcohol consumption-disease relations, together with an examination of the Comparative Risk Assessment estimates applied to the latest available revision of Global Burden of Disease study. Alcohol is causally linked (to varying degrees) to eight different cancers, with the risk increasing with the volume consumed. Similarly, alcohol use is related detrimentally to many cardiovascular outcomes, including hypertension, haemorrhagic stroke and atrial fibrillation. For other cardiovascular outcomes the relationship is more complex. Alcohol is furthermore linked to various forms of liver disease (particularly with fatty liver, alcoholic hepatitis and cirrhosis) and pancreatitis. For diabetes the relationship is also complex. Conservatively, of the global NCD-related burden of deaths, net years of life lost (YLL) and net disability adjusted life years (DALYs), 3.4 percent, 5.0 percent and 2.4 percent, respectively, can be attributed to alcohol consumption, with the burden being particularly high for cancer and liver cirrhosis. This burden is especially pronounced in countries of the former Soviet Union. It was concluded that there is a strong link between alcohol and non-communicable diseases, particularly cancer, cardiovascular disease, liver disease, pancreatitis and diabetes, and these findings support calls by the World Health Organization to implement evidence-based strategies to reduce harmful use of alcohol [141].

Tropical pancreatitis

Patients with tropical calcific pancreatitis (TCP) have multiple risk factors for developing low bone mineral density (BMD). It was studied BMD and serum 25-hydroxyvitamin D in north Indian TCP patients. In a cross-sectional study, 72 TCP patients (mean age, 31 ± 10 years) and 100 controls were studied. Serum vitamin D was measured in all subjects; BMD was measured by dual-energy x-ray absorptiometry in 56 adult patients and 4 children and compared with a reference Indian population. Mean BMD and BMD Z-scores at the lumbar spine and total hip were significantly lower in all age groups. Low bone density was present in 22 (39 %) adult patients and 3 of the 4 children studied. On multivariate analysis, BMD Z-scores were positively associated with body mass index and inversely with pancreatitis. Vitamin D deficiency (< 50 nmol/L) was equally prevalent in patients (86 %) and controls (85 %). It was concluded that despite their young age, patients with TCP have significantly low BMD. Measures to improve nutrition should be instituted in all TCP patients from an early age [142].

It was discussed an article on idiopathic chronic pancreatitis (ICP) in India in which there was reference to tropical chronic pancreatitis (TCP). TCP was a form of ICP first described in the 1960s in the south-western state of Kerala in India. Even though the etiology of this new condition was unknown, the clinical features of the new entity of chronic pancreatitis (CP) in young malnourished non-alcoholic subjects in poor tropical countries was so distinctive that, to distinguish it from alcoholic chronic pancreatitis (ACP), the term TCP came into usage without much thought into its etiological connotation and was accepted by the medical community. Logically, TCP was an idiopathic pancreatitis from the beginning; however, it differed from the then known forms of ICP in many respects. Studies into its etiology have been inconclusive. All medical scientists interested in pancreatic diseases have wondered for half a century what causes this peculiar disease which is so different from ACP, familiar to the Western world. From the scientific point of view, some insight into the etiology of TCP might help to gain a better understanding of the aetiopathogenesis of pancreatitis in general. TCP provides a good example of a complex disease that is undergoing a change in its phenotype as a result of changes in diet and lifestyle that have occurred over a couple of

decades, and offers an opportunity to study in depth the role of some of these factors in pancreatitis. Better earning power and literacy have resulted in improvement in diet, nutrition and living standards in Kerala, along with a parallel rise in alcoholism and smoking. Many patients with TCP now drink and smoke, although in smaller amounts, thus leading to a mixed clinical picture. As a consequence of these complex changes perhaps, TCP is now assuming similarity to ICP and is also being edged out by ACP. TCP was a term given more than 50 years ago to a disease that had exceptionally distinctive features at the time it was described. It has taught us a few valuable lessons. To deny retrospectively that there was no entity of TCP is historically incorrect. Rather, it should be use this opportunity to study the factors responsible for the changing phenotype of TCP and gain some insights into the factors contributing to the causation of chronic pancreatitis [143].

Concomitant liver cirrhosis

Pancreatic surgery is associated with an increased risk of postoperative complications. It was therefore investigated the impact of an additional liver function disorder on the postoperative outcome using a case-control study of patients with or without liver cirrhosis who underwent pancreatic surgery at the department. Between 1998 and 2008, 1,649 pancreatic resections were performed. Of these, 32 operations were performed in patients who also suffered from liver cirrhosis (30× Child A, 2× Child B). For the case-control study, it was selected another 32 operated patients without cirrhosis who were matched according to age, gender, diagnosis and tumor classification. The following parameters were compared between both groups: operating time, number of transfusions, duration of ICU and hospital stay, incidence of complications, rate of reoperation, mortality. Patients with cirrhosis experienced complications significantly more often (69 vs 44 %), especially major complications (47 vs 22 %) requiring reoperation (34 vs 12 %). These patients also had a prolonged hospital stay (28 vs 24 days) and a significantly longer ICU stay (9 vs 4 days), and required twice as many transfusions. Overall, 3 patients died following surgery, 1 with Child A (3 % of all Child A patients) and 2 with Child B cirrhosis. It was concluded that pancreatic surgery is associated with an increased risk of postoperative complications in patients with liver cirrhosis, and is therefore not recommended in patients with Child B cirrhosis. In Child A cirrhotic patients the mortality is, however, comparable to noncirrhotic patients. Due to the demanding medical efforts that these patients require, they should be treated exclusively in high-volume centers [144].

Thalassemia

Patients with beta-thalassemia major at risk of cardiac iron overload have to be identified to undergo myocardial iron measurements by magnetic resonance imaging (MRI), especially, in areas and centers with restricted access to MRI. Measurements of heart iron, liver iron, and pancreatic exocrine function were performed in 44 patients by MRI-R2* [the transverse relaxation rate $R2^* (= 1/T2^*)$ characterizes the magnetic resonance decay from protons not being in phase with each other in contrast to $R2 (= 1/T2)$], biomagnetic liver susceptometry (LIC), and pancreatic serum amylase (PAM) and lipase (LIP), respectively. ROC analysis (area: 0.88) for detecting patients with cardiac $R2^* > 50/\text{sec}$ ($T2^* < 20 \text{ msec}$) by LIP revealed a cut-off level of 19 U/L. In conclusion, patients at risk of elevated cardiac iron levels could be identified by the exocrine pancreatic lipase and amylase function parameters [145].

Iron endocrinopathy and cardiomyopathy are common in chronically transfused thalassaemia major patients, but relatively rare in chronically transfused patients with sickle cell disease. Since magnetic resonance imaging can demonstrate preclinical organ iron deposition, it was hypothesized that pancreas and cardiac R2 would likewise be lower in sickle cell disease patients than thalassaemia major patients having comparable transfusional burdens. To test this hypothesis, it was examined pancreatic and cardiac iron in a convenience sample of 100 chronically-transfused sickle cell disease and 131 thalassaemia major patients. Cardiac R2 and pancreatic R2 were significantly lower in sickle cell disease than thalassaemia major. Liver iron concentration was similar in both groups. The observed disparity in pancreatic and cardiac iron loading between sickle cell disease and thalassaemia major patients mirrors prior observations of organ toxicity in these patients. Greater cumulative transfusional iron exposure in thalassaemia major patients partially explains these observations but the data also suggest innate differences in labile iron handling between the two diseases [146].

Systemic lupus erythematosus

To evaluate amylase and lipase levels in a cohort of patients diagnosed with SLE, identify patients with subclinical and clinical pancreatitis and investigate factors associated demographic, clinical and laboratory data were collected, including recent clinical symptoms possibly related to pancreatitis, use of medication, disease activity (SLEDAI-2K), and serum amylase and lipase levels. Patients with pancreatic enzyme levels ≥ 1.5 times in excess of the upper limit of normal and/or patients with clinical suspicion of pancreatitis were submitted to abdominal CT or US. The study included 136 SLE patients aged 34 ± 11 years. Three patients (2 %) were diagnosed with clinical pancreatitis and 7 (5 %) with subclinical pancreatitis. Multiple causal factors were associated with increased enzymes levels such as activity of the disease, drug toxicity, hypertriglyceridemia and chronic kidney failure. Patients with clinical and subclinical pancreatitis ($n=10$) when compared with pancreatitis-free patients had more SLE active, levels were lower for haemoglobin, platelets and albumin, and higher for triglycerides and AST. Thrombocytopenia, high blood sedimentation rate and hypertriglyceridemia were the only variables associated with pancreatitis in the logistic regression model. The prevalence of clinical and subclinical pancreatitis in SLE patients was low and associated with multiple potential factors. The association of thrombocytopenia and pancreatitis in SLE patients requires further studies [147].

Pain pattern

To compare patients with chronic pancreatitis (CP) with constant pain patterns to patients with CP with intermittent pain patterns a prospective cohort study was conducted at 20 tertiary medical centers in the USA comprising 540 subjects with CP. Patients with CP were asked to identify their pain from five pain patterns (A-E) defined by the temporal nature (intermittent or constant) and the severity of the pain (mild, moderate or severe). Pain pattern types were compared with respect to a variety of demographic, quality of life (QOL) and clinical parameters. Rates of disability were the primary outcome. Secondary outcomes included: use of pain medications, days lost from school or work, hospitalisations (preceding year and lifetime) and QOL as measured using the Short Form-12 (SF-12) questionnaire. Of the 540 CP patients, 414 patients (77 %) self-identified with a particular pain pattern and were analysed. Patients with constant pain, regardless of severity, had higher rates of disability, hospitalisation and pain medication use than patients with intermittent pain. Patients with constant pain had lower QOL (by SF-12) compared with patients who had intermittent pain. Additionally, patients with constant pain were more likely to have alcohol as the etiology for their pancreatitis. There was no association between the duration of the disease and the quality or severity of the pain. The authors concluded that this is the largest

study ever conducted of pain in CP. These findings suggest that the temporal nature of pain is a more important determinant of health-related QOL and healthcare utilisation than pain severity. In contrast to previous studies, the pain associated with CP was not found to change in quality over time. These results have important implications for improving our understanding of the mechanisms underlying pain in CP and for the goals of future treatments and interventions [148].

Brain function

In patients with painful chronic pancreatitis (CP) there is increasing evidence of abnormal pain processing in the central nervous system. Using magnetic resonance (MR) diffusion tensor imaging, brain microstructure in areas involved in processing of visceral pain was characterised and these findings were correlated to clinical pain scores. Twenty-three patients with CP pain and 14 controls were studied in a 3T MR scanner. Apparent diffusion coefficient (ADC) (i.e. diffusivity of water) and fractional anisotropy (FA) (i.e. organisation of fibres) values were assessed in the amygdala, cingulate cortex, insula, prefrontal cortex and secondary sensory cortex. Daily pain scores and the Brief Pain Inventory Short Form were collected 1 week before the investigation. In grey matter, patients had increased ADC values in amygdala, cingulate cortex, insula and prefrontal cortex, as well as decreased FA values in cingulate cortex and secondary sensory cortex. In white matter, patients had increased ADC values in insula and prefrontal cortex, and decreased FA values in insula and prefrontal cortex. An effect modification from the pain pattern (attacks vs continuous pain) was seen in the insula and secondary sensory cortex, but no effect modifications from diabetes, alcoholic aetiology and opioid treatment were seen. Microstructural changes in cingulate and prefrontal cortices were correlated to patients' clinical pain scores. The findings suggest that microstructural changes of the brain accompany pain in CP. The changes are likely to be a consequence of ongoing pain and structural reorganisation of the neuromatrix as also seen in other diseases characterised by chronic pain [149].

Risk of pancreatic cancer

It is suggested that patients with chronic pancreatitis (CP) have a markedly increased risk of pancreatic cancer compared with the general population. One study was designed to determine the rate of pancreatic cancer in CP patients in China. It was a semipropective, single-center study including 420 consecutive CP patients (285 males and 135 females, median age at onset 40 years), with the median follow-up time being 102 months (range 24-419 months). It was calculated the standardized incidence ratio (SIR) based on the pancreatic cancer incidence in the general population of China. Four cases of pancreatic cancer (0.9 % of patients) were observed in 3,591 patient-years (expected number of cases 0.15; SIR 27, 95 % confidence interval 7 to 70). Similar results were seen in alcoholics and non-alcoholics, and in smokers and non-smokers. When patients lost to follow-up were considered to be followed up until the end point without having developed pancreatic cancer (4,280 patient-years), SIR was 23 (95 % confidence interval 6 to 58). Based on the Cox model, with inserting factors being gender, age at the time of CP clinical onset, type of pancreatitis, and presence or absence of diabetes, calcification, alcohol use and smoking status, only age was found to correlate positively with the occurrence of pancreatic cancer (>50 years, hazard ratio, 1.8 ± 0.5). It was concluded that the risk of pancreatic cancer is markedly increased in CP patients in China compared with the general population, especially in older patients [150].

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Differential diagnosis from pancreatic cancer

It is difficult to distinguish pancreatic ductal adenocarcinoma (PDAC) from chronic pancreatitis (CP) when stricture is present in the pancreatic duct. Endoscopic brushing cytology is a convenient method for investigating strictures in the pancreatic duct, however, the diagnostic sensitivity of this method for PDAC is reported to be low (40-70 %). Recently, we revealed that MSX2 is frequently expressed in PDAC cells but not in normal cultured pancreatic duct or stellate cells. Thus, we analyzed MSX2 expression levels in brushing samples to examine whether this would differentiate PDAC from CP. Cytologic brushing specimens were obtained from pancreatic duct strictures during endoscopic retrograde cholangiopancreatography in 82 patients. The brushing fluid was subjected to cytological diagnosis and RNA extraction. The expression level of MSX2 was evaluated by one-step real-time RT-PCR. MSX2 expression levels were significantly higher in PDAC than in CP and the expression level was associated with positive cytology. The sensitivity, specificity, and diagnostic accuracy for PDAC of cytology and MSX2 expression in ductal strictures were: 47, 100, and 63, and 74, 84, and 79 percent, respectively. The sensitivity and accuracy of MSX2 expression levels for diagnosis were much higher than those of cytology. This suggests that the evaluation of MSX2 levels in endoscopic retrograde cholangiopancreatography brushing samples would be useful for distinguishing pancreatic cancer from chronic pancreatitis [152].

Molecular markers of angiogenesis

Discrimination between pancreatic cancer and chronic pancreatitis may be made by conventional serum tumor marker (CA19-9) and imaging techniques. Angiogenesis is a critical process for tumor growth and metastasis and involves the changes in the balance between angiogenic growth factors and angiogenesis inhibitors. However, because angiogenesis is composed of multistep processes controlled by various factors, the role of angiogenesis in pancreatic cancer has not been fully elucidated. One study was conducted to determine whether the concentrations of a set of 8 angiogenic molecules (platelet-derived growth factor-BB, vascular endothelial growth factor, basic fibroblast growth factor, angiogenin, keratinocyte growth factor (KGF), tissue inhibitor of metalloproteinase- 1 (TIMP-1), intercellular adhesion molecule- 1, and angiopoietin-2) in serum can be used as a noninvasive diagnostic test for pancreatic cancer. Within 10 months, it was included patients in 3 groups: pancreatic cancer (n=22), chronic pancreatitis (n=10), and healthy controls (n=24). The results show that there are significant serum concentration differences between pancreatic cancer (PC), chronic pancreatitis (CP), and control groups for two molecules,

angiopoietin (ANGT)-2 and vascular endothelial growth factor (VEGF). Regarding the ANGT-2, the results have shown significant higher levels in PC and CP than in the control group and statistically significant between the PC and CP groups. In addition, VEGF was lower in the control group than in the PC and CP groups. Regarding platelet-derived growth factor-BB, fibroblast growth factor-B, tissue inhibitor of metalloproteinase-1, and intercellular adhesion molecule-1, the other molecules investigated, it was obtained no difference between CP and PC compared with the control group. The discrimination between CP and PC is often very difficult because of the same clinical presentation and the difficulty to obtain the biopsy from pancreatic lesions. On the other hand, the association between CP and PC is now clearly established and justifies the importance of follow-up of the patients with chronic pancreatitis. The pathway between chronic inflammation and cancer involves many steps including various cytokines, reactive oxygen species, mediators of the inflammatory pathway, which increase genomic damage, and cellular proliferation with malignant transformation of pancreatic cells. Recent studies suggest that there are significantly more mast cells and macrophages in pancreatic cancer than in normal pancreas, which express VEGF-A, VEGFC, and bFGF and contribute to the development of tumors with high angiogenic activity. Previous studies have shown that VEGF is a key component in pancreatic tumorigenesis, its high expression levels being correlated with poor prognosis and early postoperative recurrence. In addition, it seems that angiotensin II increases the production of VEGF through an angiotensin II type receptor and extracellular signal-regulated kinases 1/2 signaling pathway, and more ANGT-2/VEGF induction can be inhibited by an angiotensin II type 1 receptor (AT1R) antagonist or angiotensin I-converting enzyme inhibitors, decreasing the development of tumor-feeding blood vessels. The results suggest that ANG-2 might represent a key molecule involved in the passage of CP to PC and could be helpful in the differentiation between PC and CP. The use of drugs that inhibit the angiotensin II pathways by controlling the growth and spread of cancer could prevent the conversion of CP into PC [153].

Angiotensin II

Pancreatic cancers often develop in the context of pancreatic fibrosis caused by chronic pancreas inflammation, which also results in the accumulation of reactive oxygen species (ROS), pancreatic parenchymal cell death, and stellate cell activation. Angiotensin II, which is converted from angiotensin I by the angiotensin-converting enzyme (ACE), stimulates ROS production via NADPH oxidase. In stellate cells, angiotensin II activates the stress-activated protein kinase p38. However, the molecular mechanism by which angiotensin II regulates pancreatic inflammation and fibrosis remains to be determined. Wistar Bonn/Kobori (WBN/Kob) rats spontaneously develop chronic pancreatic inflammation. To examine whether blockade of the renin-angiotensin system affects the development of pancreatic fibrosis, WBN/Kob rats were given angiotensin II type 1 receptor (AT1R) blocker or ACE inhibitor (ACEI). Next, it was assessed the role of angiotensin II and its possible downstream target p38 α in stellate cell activation using primary stellate cells. Treatment with AT1R blocker and ACEI prevented the development of chronic pancreatitis and fibrosis. In stellate cells, angiotensin II upregulated the expression of angiotensin II receptors, alpha-smooth muscle actin (SMA) and transforming growth factor-beta. In addition, p38 α was found to be essential to collagen type I production and alpha-SMA expression. ROS accumulation is enhanced in chronic pancreatic inflammation, which increases the risk of pancreatic cancer. Inhibition of the angiotensin II signaling pathway might be a promising strategy to prevent pancreatic fibrogenesis and subsequent carcinogenesis [154].

Hemosuccus pancreaticus

Pancreatic pseudocysts are defined as localized pancreatic fluid collections that are surrounded by fibrous tissue and are located in or around pancreatic tissue. Over time, these fluid collections may regress spontaneously but many times will persist or increase in size. The proteolytic enzyme release can also lead to the formation of pseudoaneurysms with resulting upper gastrointestinal (UGI) bleeding from the pseudoaneurysm eroding into the pancreatic duct, the so-called hemosuccus pancreaticus. The aim of one report was to present another mechanism of UGI bleeding from a pseudoaneurysm via erosion into the duodenum with creation of a fistula and its management. Gastrointestinal bleeding can be seen in 6 to 31 percent of patients with a history of chronic pancreatitis that is complicated with the formation of a pancreatic pseudocyst. An uncommon cause of bleeding in this setting is from a ruptured pseudoaneurysm that bleeds into the pseudocyst. The blood most often communicates to the ampulla of Vater via the pancreatic duct, the so-called hemosuccus pancreaticus. A rare second mechanism of UGI bleeding is that of a pseudocyst that has blood within it entering the GI tract through a gastric fistula. The management of this complication parallels the established management of hemosuccus pancreaticus. First, an upper endoscopy was urgently performed, which identified an active site of bleeding, in our case the periampullary fistula [155].

Pancreatic enzyme treatment

Exocrine (PI) requires treatment with pancreatic enzyme supplementation (i.e. pancreatin) to reduce morbidity and mortality. Whereas most pancreatin preparations contain comparable amounts of lipase, amylase, and protease in an acid-stable/enteric-coated microsphere, variations have been reported in the diameter size of these microspheres, which will affect their pyloric transit time, bioavailability, and enzymatic activity. Some studies suggest that pancreatin preparations with microsphere diameters larger than 1.7 mm pass through the stomach more slowly than food and may be less effective in providing enzymatic activity than smaller formulations. A recent paper indicated approximately 90 percent of Creon® microspheres (Solvay Pharmaceuticals, Hannover, Germany) have a diameter smaller than 1.7 mm, whereas 7 of the other 9 pancreatin preparations that were examined, including Panzytra® had a diameter between 1.9 and 2.2 mm. The study by Meyer et al concluded that microspheres with diameters of 1.4 mm ideally pass through the pylorus and provide maximal enzymatic activity in healthy volunteers. However, the gastrointestinal conditions in these subjects may not accurately represent conditions that are encountered in patients with PI, and intersubject variability was a key issue. Microspheres 1.6 mm in diameter exited the stomach faster, slower, and at the same time as coingested food in the population examined. Data from other studies suggest that a broader range of pancreatin microsphere diameters may be acceptable for promoting proper digestion and absorption in patients with PI and steatorrhea [156].

EUR-1008 (ZENPEP®, pancrelipase, delayed-release capsules) a delayed-release capsules is a novel, enteric-coated, porcine-derived pancreatic enzyme product. One study evaluated the efficacy and safety of 2 doses of ZENPEP in patients with chronic pancreatitis (CP) and exocrine pancreatic insufficiency (EPI). Methods: The effect of ZENPEP on the coefficient of fat absorption (CFA) was investigated in a randomized, double-blind, dose-response, crossover study with placebo run-in (7-9 days) and 2 treatment periods (9-11 days) composed of a high dose (7 x 20,000 lipase units per day) and a low dose (7 x 5000 lipase units per day). Mean CFA was significantly higher with low- (89 %) and high-dose (90 %) ZENPEP versus placebo run-in (82 %; n = 72) with no difference between doses. In patients with baseline CFA less than 90 percent (n=33), the high dose was significantly more effective (CFA: 84 %) than the low dose (CFA: 81 %). Post hoc analysis revealed an increase in

treatment effect with more severe EPI. Coefficient of nitrogen absorption, body weight, and body mass index also increased significantly with both doses compared with baseline. Percentage of days with EPI symptoms decreased with both doses. It was suggested that CP patients with EPI benefit from a low dose of ZENPEP, whereas the high dose might be needed for patients with more severe EPI [157].

Treatment with placebo

When either interventional or medical treatment is tested against placebo, patients with pancreatitis or presumed pancreaticobiliary pain have a high placebo response rate. For example, in patients with type 2 and 3 sphincter of Oddi dysfunction, Wilcox reported a 38 percent endoscopic placebo response rate. In patients with abdominal pain and CP, others reported a similar 35 percent placebo response rate in trials of octreotide versus placebo or the cholecystokinin-A receptor antagonist loxiglumide versus placebo. Also, patients with CP have a dramatic, but less quantifiable, placebo response in a trial of antioxidants versus placebo. These 35-38 percent placebo response rates are strikingly similar to the 32 percent “therapeutic response” of endoscopic drainage of the pancreatic duct in a randomized controlled trial of patients with large-duct CP. Recognition of the placebo response led Cooperman et al to comment that it remains unclear whether a perceived therapeutic response to dorsal duct drainage procedures in patients with PD represents “...a satisfactory result, stabilization of the disease, symbiosis between patient and symptoms, or fear of admitting persistent symptoms...” Hence, only properly randomized and controlled trials of treatment versus no treatment will determine whether endoscopic therapy is effective for reducing pain in patients with chronic pancreatitis [158].

Endoscopic versus surgical drainage of the pancreatic duct

A randomized trial that compared endoscopic and surgical drainage of the pancreatic duct in patients with advanced chronic pancreatitis reported a significant benefit of surgery after a 2-year follow-up period. It was evaluated the long-term outcome of these patients after 5 years. Between 2000 and 2004, 39 symptomatic patients were randomly assigned to groups that underwent endoscopic drainage or operative pancreaticojejunostomy. In 2009, information was collected regarding pain, quality of life, morbidity, mortality, length of hospital stay, number of procedures undergone, changes in pancreatic function, and costs. Analysis was performed according to an intention-to-treat principle. During the 79-month follow-up period, one patient was lost and 7 died from unrelated causes. Of the patients treated by endoscopy, 68 percent required additional drainage compared with 5 percent in the surgery group. Hospital stay and costs were comparable, but overall, patients assigned to endoscopy underwent more procedures (median, 12 vs 4). Moreover, 47 percent of the patients in the endoscopy group eventually underwent surgery. Although the mean difference in Izbicki pain scores was no longer significant (39 vs 22), surgery was still superior in terms of pain relief (80 % vs 38 %). Levels of quality of life and pancreatic function were comparable. In the long term, 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. Importantly, almost half of the patients who were treated with endoscopy eventually underwent surgery [159].

Surgery

Chronic pancreatitis (CP) is a benign inflammatory process, which can cause enlargement of the pancreatic head accompanied by severe pain and weight loss, and often leads to a

significant reduction in quality of life (QoL). Basically, the disease is characterised by pain and functional disorders which are initially treated with conservative therapy, but in case of complications (uncontrollable pain or obstruction) surgical treatment is required. One article reviewed the relevant literature of CP treatment, in particular randomized controlled trials and meta-analyses were involved with a comparison of different surgical treatment options for the management of CP complications. Recent studies have demonstrated that surgical procedures are superior to endoscopic therapy as regards long-term results of QoL and pain control. There was no significant difference found in postoperative pain relief and overall mortality when duodenum-preserving pancreatic head resection (DPPHR) of Beger and its modification (duodenum and organ-preserving pancreatic head resection, DOPPHR) were compared with pancreateoduodenectomy (PD), but hospital stay, weight gain, exocrine and endocrine insufficiency, and QoL were significantly better in the DPPHR and DOPPHR groups. DPPHR and pancreateoduodenectomy seem to be equally effective in terms of postoperative pain relief and overall mortality. However, recent data suggest that DOPPHR is superior in the treatment of CP with regard to several peri- and postoperative outcome parameters and QoL. Therefore, this should be the preferable treatment option for CP complications [160].

Lateral pancreatojejunostomy

Chronic pancreatitis is mainly managed with drugs, but surgery is required in selected groups of patients. The Partington procedure is still the procedure of choice for patients with a dilated main pancreatic duct but without an inflammatory pancreatic head mass. The same equivalent can be achieved by laparoscopic approach. Laparoendoscopic single-site surgery gained tremendous attention in the past few years. Complex surgeries are being reported using this technique. It was reported in one paper the first laparoendoscopic single-site lateral pancreatojejunostomy (LPJ) for chronic calcific pancreatitis with dilated pancreatic duct. The procedure was performed on a 32-year-old female diagnosed to have chronic calcific pancreatitis. A single vertical 2.5-cm umbilical incision and one 10-mm and two 5-mm ports were made. The procedure was completed in 220 min without any intraoperative complication. There were no postoperative complications, and the patient was discharged on day 5 when she started taking routine diet. This preliminary experience suggests that single-incision laparoscopic LPJ is feasible and safe when performed by an experienced laparoscopic surgeon. It has a cosmetic advantage over laparoscopic LPJ. However, it remains to be determined if this technique offers additional advantages of decreased analgesia, decreased hospital stay or cost effectiveness. Further studies are required to analyze these factors [161].

Islet autotransplantation after extended pancreatectomy

Extended pancreatectomy is associated with the risk of surgical diabetes. Islet autotransplantation is successful in the prevention of diabetes after pancreas resection for chronic pancreatitis (CP), with insulin independence rates of 50 percent at 1 year. The aim of the present study was to demonstrate the safety and efficiency of islet autotransplantation after extended left pancreatectomy for benign disease. Between 1992 and 2009, 25 patients underwent extended pancreatectomy and islet autotransplantation for benign disease. Of these, 15 patients were operated for focal lesions located at the neck of the pancreas (14 benign tumors and 1 traumatic pancreatic section), the remainder being CP cases. After unequivocal diagnosis of benignity, the rest of the pancreas was processed and infused into the portal vein. Metabolic results were analyzed and isolation results were compared with those obtained from patients with CP or donors with brain death (DBD). There was no mortality and a low morbidity (Streptococcus mitis bacteremia in 1 patient), no portal thrombosis or pancreatic fistula occurred. Median follow-up was 90 months. Actuarial patient survival was 100 percent at 10 years. Actuarial insulin independence was 94 percent at 10

years. All patients had positive basal and stimulated C-peptide levels and normal HbA1c. Mean islet yields were 5455 IEQ/gram vs. 1457 in CP and 3738 in DBD. It was concluded that islet autotransplantation after extensive pancreatic resection for benign disease is a safe and successful procedure. Islet yields after isolation, which are equivalent to the live donor situation, are significantly better than those from DBD donors [162].

The number of islets available (yield) is an important predictor of insulin independence after islet autotransplantation (IAT) done at the time of total pancreatectomy to treat painful chronic pancreatitis. The aim of one study was to correlate histopathologic findings with islet yield and graft function. Pancreatic histopathology was examined in 105 adults who underwent pancreatectomy and IAT; postoperative insulin use was known in 53 cases. Histologic degree of fibrosis, acinar atrophy, inflammation, and nesidioblastosis were scored by a surgical pathologist. The correlation of histopathology with islet yield and graft function was evaluated. Patients received a median of 2968 islet equivalents per kilogram. Fibrosis and acinar atrophy correlated negatively with islet yield, as did inflammation. There was a positive correlation of islet yield and a negative correlation of fibrosis and acinar atrophy with islet graft function. It was concluded that more severe histopathologic changes were associated with a lower islet yield and lower likelihood of insulin independence. Total pancreatectomy and IAT should not be delayed in patients with painful chronic pancreatitis refractory to medical therapy; otherwise progressive damage to the pancreas may limit islet yield and increase the risk of diabetes [163].

Use of the recanalised umbilical vein for transplantation

Islet autotransplantation requires access to the portal vein or tributaries. It was originally infused islets into the liver via the middle or right colic veins, but since 2005 one group has used the recanalised umbilical vein. It was now described the technique, the advantages and the early results achieved. After removal of the pancreas and restoration of the biliary and enteric continuity, the ligamentum teres is transected. The obliterated umbilical vein is identified and recanalised with Bakes dilators giving access to the left portal vein. A 11-Fr catheter is inserted and used for the islet infusion. If the ligamentum teres is to be exteriorised for postoperative measurements or subsequent access, it is pulled through a 10-mm laparoscopic port in the epigastrium, sutured to the skin and covered with a dressing. It has been used this approach in 17 patients and exteriorised the falciform ligament in 4. There have been no intra- or postoperative complications. The authors concluded that the recanalised umbilical approach is safe and allows for venous sampling and postoperative measurements of the portal pressure. Under local anaesthetic, the umbilical vein can be approached above the umbilicus and exteriorised if repeated transplants are required for allograft patients [164].

ESWL

Extracorporeal shock wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) are used to clear main pancreatic duct (MPD) stones and alleviate pain in patients with chronic pancreatitis. The goal of one study was to determine if delayed ERCP after disintegration of MPD stones with ESWL improves the successful clearance of the MPD. Adult patients with chronic pancreatitis who underwent ESWL for stone disintegration were identified from an ESWL database at a single tertiary referral center. The complete clearance of stones from the MPD with ERCP performed less than 2 days after ESWL was compared to complete clearance from ERCP more than 2 days after ESWL. Nineteen patients underwent ERCP less than 2 days after ESWL, and 3 (16 %) of the 19 achieved MPD clearance. Eleven patients underwent ERCP more than 2 days after ESWL, and 9 (82%) of 11 patients achieved MPD clearance, which was a significant difference. In total, 19 of 30 ERCPs were performed less than 2 days after ESWL, and 84 percent failed to

clear the MPD. The timing of ERCP after ESWL may be important to successfully clear stones from the MPD. This study shows that ERCP performed less than 2 days after ESWL may be more likely to fail, possibly owing to ESWL-induced edema. Delaying ERCP after ESWL may allow tissue recovery after ESWL [165].

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is a newly developed concept for a peculiar type of pancreatitis, and at present is recognized as a pancreatic lesion reflecting IgG4-related systemic disease. It is of utmost importance to differentiate AIP from pancreatic cancer to avoid unnecessary surgery. The current management strategies for AIP, including its clinical features, diagnostic criteria, clinical subtypes, steroid therapy and prognosis were discussed, based on our 66 AIP cases and papers searched in PubMed from 1992 to March 2011, using the term "autoimmune pancreatitis". AIP should be considered in the differential diagnosis in elderly male patients presented with obstructive jaundice and pancreatic mass. Steroids are a standard therapy for AIP, but their regimen including maintenance therapy should be evaluated in prospective trials [166].

Since the revision of Clinical Diagnostic Criteria for Autoimmune Pancreatitis (AIP) 2006, many cases of localized AIP have been reported. Localized AIP is often difficult to preoperatively differentiate from pancreatic carcinoma. It was presented two cases of localized AIP that developing relapse after surgical treatment. Swollen hilar lymph nodes of lung were detected on CT in both two cases. Recently, AIP is thought to be the pancreatic manifestation of an IgG4 related systemic disease, which has been associated with many extrapancreatic lesions. Response to steroid treatment and the detection of extrapancreatic lesions may contribute to provide adequate diagnosis thereby avoiding unnecessary surgery [167].

IgG4-related systemic disease is an autoimmune disease that was first recognized in the pancreas but also affects other organs. This disease may manifest as tubulointerstitial nephritis (IgG4-TIN), but its clinicopathologic features in the kidney are not well described. Of the 35 patients with IgG4-TIN whose renal tissue specimens we examined, 27 (77 %) had acute or progressive chronic renal failure, 29 (83 %) had involvement of other organ systems, and 18 of 23 (78 %) had radiographic abnormalities. Elevated total IgG or IgG4 serum levels were present in 79 percent. All pathologic specimens featured plasma cell-rich TIN, with most showing diffuse, expansile interstitial fibrosis. Immune complexes along the tubular basement membranes were present in 25 of 30 (83 %). All specimens had a moderate to marked increase in IgG4+ plasma cells by immunohistochemistry. We used a control group of 175 pathologic specimens with plasma cell-rich interstitial infiltrates that can mimic IgG4-TIN to examine the diagnostic utility of IgG4 immunostaining. Excluding pauci-immune necrotizing and crescentic glomerulonephritis, IgG4 immunohistochemistry had a sensitivity of 100 percent (95 % confidence interval 90 to 100 %) and a specificity of 92 percent (95 % confidence interval 86 to 95 %) for IgG4-TIN. Of the 19 patients with renal failure for whom treatment and follow-up data were available, 17 (89 %) responded to prednisone. In summary, because no single test definitively diagnoses IgG4-related systemic disease, it must be relied on a combination of histologic, immunophenotypic, clinical, radiographic, and laboratory features. When the disease manifests in the kidney, the data support diagnostic criteria that can distinguish IgG4-TIN from other types of TIN [168].

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis with a discrete pathophysiology, occasional diagnostic radiological findings, and characteristic histological features. Sarles et al in 1961 were the first to use the term "autoimmune" in an attempt to clarify the etiology of "chronic inflammatory sclerosis of the pancreas". Since then, the

disease has been referred to as sclerosing pancreatitis, primary inflammatory pancreatitis, non-alcoholic duct-destructive chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis, chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct, sclerosing pancreatocholangitis, and inflammatory pseudotumor. The term "autoimmune pancreatitis" (AIP) was eventually proposed by Yoshida et al in 1995, who reported a case of chronic pancreatitis with hyperglobulinemia and serum autoantibodies responding to corticosteroid therapy. Current opinions agree that AIP is the pancreatic manifestation of a systemic autoimmune disease, affecting many other organs and causing lesions with common histological features and almost similar microscopic architecture. AIP is more common in males and the usual age of presentation is the 6th decade of life, although sporadic cases have been described even from the age of 20. Recently, two types of AIP have been distinguished, type 1 or lymphoplasmacytic sclerosing pancreatitis (LPSP) and type 2 or idiopathic duct centric pancreatitis (IDCP) or granulocyte epithelial lesion (GEL). Autoimmunity is probably implicated in the pathogenesis of AIP as indicated mainly by specific serologic abnormalities (presence of autoantibodies and elevated levels of gamma-globulin) and secondarily by the dramatic response observed after steroid therapy. Antibodies against lactoferrin and carbonic anhydrase-II and IV are the most frequently detected autoantibodies in AIP (73 % and 54 % respectively). Antibodies against pancreatic secretory trypsin inhibitor (PSTI) are additionally detected in 30-40 percent of cases. Patients may also have autoantibodies against rheumatoid factor, smooth muscle antigens, and nuclear antigens. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is expressed on activated T-cells, regulates T-cell stimulation and single-nucleotide polymorphisms identified in CTLA-4 are associated with susceptibility to autoimmune diseases. Moreover, Fc receptor-like 3 (FCRL3) polymorphisms (expressed on B-cells) have also been shown to contribute to autoimmune mechanisms. Elevated levels of gamma-globulin in the serum is a characteristic finding in type 1 AIP. The majority of these antibodies belong to the IgG4 subclass, which normally accounts for 3-6 percent of total serum IgG but is significantly increased in AIP [169].

Definitions

To achieve the goal of developing international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP) an international panel of experts met during the 14th Congress of the International Association of Pancreatology held in Fukuoka, Japan, from July 11 through 13, 2010. The proposed criteria represent a consensus opinion of the working group. Autoimmune pancreatitis was classified into types 1 and 2. The ICDC used 5 cardinal features of AIP, namely, imaging of pancreatic parenchyma and duct, serology, other organ involvement, pancreatic histology, and an optional criterion of response to steroid therapy. Each feature was categorized as level 1 and 2 findings depending on the diagnostic reliability. The diagnosis of type 1 and type 2 AIP can be definitive or probable, and in some cases, the distinction between the subtypes may not be possible (AIP-not otherwise specified). The ICDC for AIP were developed based on the agreement of an international panel of experts in the hope that they will promote worldwide recognition of AIP. The categorization of AIP into types 1 and 2 should be helpful for further clarification of the clinical features, pathogenesis, and natural history of these diseases [170].

Two types

Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of the pancreas. Examination of pancreatic resection specimens from patients with AIP has shown that there are 2 subclasses of this disease. However, there is no widely accepted pathologic classification scheme and the clinical significance of such a classification remains to be

established. In one study, it was revisited the subclassification of AIP and examine whether this provides clinically and prognostically meaningful information. It was evaluated 29 pancreatic resection specimens from patients with AIP. Demographic, clinical, and imaging data were recorded, as was evidence of extrapancreatic manifestations. In addition to a detailed and semiquantitative histologic evaluation, immunohistochemistry for IgG4 was performed on pancreatic and extrapancreatic tissues. It was also evaluated 48 consecutive cases of chronic pancreatitis, not otherwise specified. The resected specimens could readily be subclassified into 2 subtypes: type 1 (n=11) and type 2 (n=18). In comparison with patients with type 2 disease, patients with type 1 disease were significantly more likely to be males, older, and present with jaundice, and less likely to be associated with abdominal pain. On imaging, the pancreatic tail cut-off sign was exclusively seen in patients with type 2 disease (4 of 10 cases). Hypercellular inflamed interlobular stroma was unique to type 1 pattern (91 %), whereas significant ductal injury in the form of microabscesses and ductal ulceration was almost exclusively seen in type 2 pattern (78 %). Eight of 10 patients with a type 1 pattern had evidence of a systemic disease. Three patients with type 2 disease had recurrent episodes of pancreatitis after their pancreatic resection. In comparison with the cohort of chronic pancreatitis, not otherwise specified, type 2 AIP cases were less likely to be associated with a history of alcohol abuse, and showed significantly more foci of periductal inflammation and neutrophilic microabscesses. The review of pancreatic resection specimens showed 2 histologically distinct forms of AIP. Our data support the concept that type 1 AIP is a systemic disease and is the pancreatic manifestation of IgG4-related systemic disease. Type 2 disease is confined to the pancreas. The intensity of the periductal inflammatory infiltrate and the presence of ductal neutrophilic abscesses are features that assist in distinguishing type 2 AIP from chronic pancreatitis, not otherwise specified. Although imperfect, clinical and imaging features may help distinguish the 2 subtypes of AIP. On the basis of these significant differences between the 2 types of AIP, it was advocated the position that all subsequent studies attempt to substratify their patients into these 2 groups [171].

Autoimmune pancreatitis (AIP) is better described than before, but there is still no international consensus for definition, diagnosis, and treatment. The aims were now to analyze the short- and long-term outcome of patients with focus on pancreatic endocrine and exocrine functions, to search for predictive factors of relapse and pancreatic insufficiency, and to compare patients with type 1 and type 2 AIP. All consecutive patients followed up for AIP in our center between 1999 and 2008 were included. Two groups were defined: patients with type 1 AIP meeting HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to steroids) criteria; and patients with definitive/probable type 2 AIP including those with histologically confirmed idiopathic duct-centric pancreatitis ("definitive") or suggestive imaging, normal serum IgG4, and response to steroids ("probable"). AIP-related events and pancreatic exocrine/endocrine insufficiency were looked for during follow-up. Predictive factors of relapse and pancreatic insufficiency were analyzed. A total of 44 patients (22 males), median age 38 (19-73) years, were included: 28 patients (64 %) with type 1 AIP and 16 patients (36 %) with type 2 AIP. First-line treatment consisted of steroids or pancreatic resection in 59 and 27 percent of the patients, respectively. Median follow-up was 41 (5-130) months. Steroids were effective in all treated patients. Relapse was observed in 12 patients (27 %), after a median delay of 6 months (1-70). Four patients received azathioprine because of steroid resistance/dependence. High serum IgG4 level, pain at time of diagnosis, and other organ involvement were associated with relapse. At the end point, pancreatic atrophy was observed in 35 percent of patients. Exocrine and endocrine insufficiencies were present in 34 and 39 percent of the patients, respectively. At univariate analysis, no factor was associated with exocrine insufficiency, although female gender, increasing age, and type 1 AIP were associated with the occurrence of diabetes. Steroid/azathioprine treatment did not prevent pancreatic insufficiency. Type 2 AIP was more frequently associated with inflammatory bowel disease than type 1 AIP (31 and 3 %, respectively), but relapse rates were similar in both groups. It was concluded that the relapse

occurs in 27 percent of AIP patients and is more frequent in patients with high serum IgG4 levels at the time of diagnosis. Pancreatic atrophy and functional insufficiency occur in more than one-third of the patients within 3 years of diagnosis. The outcome of patients with type 2 AIP, a condition often associated with inflammatory bowel disease, is not different from that of patients with type 1 AIP, except for diabetes [172].

Etiology and risk factors

Genetic studies have suggested that several human leukocyte antigen (HLA) and non-HLA haplotypes/genotypes are associated with susceptibility to IgG4-related disease or to disease relapse after steroid therapy. Among several autoantibodies identified so far, autoantibodies against lactoferrin and carbonic anhydrase II are most frequently detected in serum of IgG4-disease patients. However, it has not been well clarified whether or not those autoantibodies belong to an IgG4 subclass. Studies that have demonstrated molecular mimicry between *Helicobacter pylori* and constituents of pancreatic epithelial cells suggest that gastric *H. pylori* infection triggers autoimmune pancreatitis in genetically predisposed individuals through antibody cross-reactivity. Recently, T-helper 2 immune reaction has been suggested to be predominant in IgG4-related disease. Interestingly, regulatory immune reactions are activated in IgG4-related disease, and regulatory cytokines interleukin-10 and transforming growth factor- β have been suggested, respectively, to play important roles in IgG4 class switch and fibroplasia. Autoimmunity has been considered the most probable pathogenesis of IgG4-related disease, but has not been completely proved so far. A breakthrough study to detect a specific autoantigen, autoantibody, or pathogen is necessary [173].

IgG4

IgG4-related systemic disease (ISD) is a recently recognized syndrome affecting multiple organs. Autoimmune pancreatitis (AIP) is the pancreatic manifestation of ISD and mimics pancreatic cancer. Current data show frequent association with serum IgG4 elevation and other serologic abnormalities. Here we explore the diagnostic and possible prognostic utility and pathogenetic implications of serologic abnormalities in ISD. Serum IgG4 elevations (>140 mg/dL) are seen in 70-80 percent of AIP patients and also in 5 percent of normal population and 10 percent of pancreatic cancer making it an unsuitable single marker for diagnosis. However, when combined with other features of AIP, it can be of great diagnostic value though its utility in monitoring of therapy or as a marker or predictor of relapse is limited. Several other antibodies have been identified in AIP against pancreas-specific antigens like trypsinogens I and II, pancreatic secretory trypsin inhibitor (PSTI) and plasminogen binding protein (PBP) and other nonpancreas-specific antigens. Anti-PBP antibodies appear to have potential diagnostic utility but require further validation. It was concluded that no single serologic marker is diagnostic of ISD. Serum IgG4 elevation has convincing diagnostic utility when combined with other disease features although its value in disease monitoring may be limited [174].

Regulatory T-cells

Immunoglobulin G4 (IgG4)-related autoimmune pancreatitis (AIP) is a new clinical entity of pancreatic disorder. There are immunologic and histological abnormalities, including increased serum IgG4 levels and the infiltration of IgG4-positive plasmacytes. However, the role of IgG4 is unclear. Recently, regulatory T cells (Tregs) were reported to contribute to the development of various autoimmune diseases as well as in B-cell shifting to IgG4-producing plasmacytes. It was studied Tregs in the pancreas and peripheral blood. It was recruited 44 patients with IgG4-related AIP. For comparison, it was recruited 37 patients with other pancreatic diseases and 27 healthy subjects as controls. We studied infiltrating cells in the

pancreas by immunohistochemistry and analyzed inducible costimulator-positive Tregs and interleukin 10-positive Tregs in the peripheral blood by flow cytometry. The ratio of Foxp3-positive cells to infiltrated mononuclear cells (Foxp3/Mono) in AIP patients was significantly higher than in patients with alcoholic chronic pancreatitis. In AIP, Foxp3/Mono and IgG4/Mono were positively correlated. Inducible costimulator-positive Tregs were significantly higher in AIP patients than in the patients with other pancreatic diseases and the healthy control group. Interleukin 10-positive Tregs were significantly higher in AIP patients than in the healthy control group. It was concluded that increased quantities of inducible costimulator-positive Tregs may influence IgG4 production in IgG4-related AIP [175].

Helicobacter

In 2005, Guarneri et al claimed the possible involvement of *Helicobacter pylori* in the stimulation of the autoimmune process in AIP as indicated by the significant homology found between human carbonic anhydrase-II and alpha-carbonic anhydrase of *H. pylori*. According to this hypothesis, patients with *H. pylori* infection are susceptible to developing AIP via molecular mimicry. Frulloni et al discovered that 94 percent of patients with AIP have antibodies against the plasminogen-binding protein of *H. pylori*, which reinforces this hypothesis [169].

Demography

To date, most cases of autoimmune pancreatitis (AIP) have been reported from Japan. The aim of one study was to assess the clinical features and management of AIP cases in Hungary. The demographics, clinical presentation, laboratory and imaging findings, extrapancreatic involvement, treatment response and recurrence were evaluated in the first 17 patients diagnosed with AIP in Hungary. The mean age at presentation was 43 years (range: 16–74); 47 percent of the patients were women. New-onset mild abdominal pain (76 %), weight loss (41 %) and jaundice (41 %) were the most common symptoms, with inflammatory bowel disease being the most frequent (36 %) extrapancreatic manifestation. Diffuse pancreatic swelling was seen in 7 patients (41 %) and a focal pancreatic mass in 8 (47 %). Endoscopic retrograde cholangiopancreatography revealed pancreatic duct strictures in all study patients. The serum IgG4 level at presentation was elevated in 62 percent of the 8 patients in whom it was measured. All the percutaneous core biopsies (5 patients) and surgical specimens (2 patients), and 2 of the 4 biopsies of the papilla of Vater revealed the typical characteristic findings of AIP: a diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis and obliterative phlebitis. Immunostaining indicated IgG4-positive plasma cells in 62 percent of the 8 patients in whom it was performed. Granulocytic epithelial lesions (GEL) were present in 3 patients. The patients without GELs were older (mean age 59 years), while those with GEL were younger (mean age 34 years), and 2 of 3 were female and had ulcerative colitis. A complete response to steroid treatment was achieved in all 15 patients. Because of the suspicion of a pancreatic tumor, 2 patients with focal AIP underwent partial pancreatectomy. One patient relapsed, but responded to azathioprine. This means that this first Hungarian series has confirmed several previously reported findings on AIP. AIP with GEL was relatively frequent among our patients: these patients tended to be younger than in earlier studies and displayed a female preponderance with a high coincidence of ulcerative colitis. Performance of a percutaneous biopsy is strongly recommended. The response to immunosuppressive therapy was excellent [176].

Symptoms and signs

AIP usually manifests either as acute or chronic symptomatic pancreatitis. However, in many cases the predominant symptoms derive from extra-pancreatic disease. The acute syndrome may appear with jaundice (40-80 %), diabetes mellitus (40-70 %), mild abdominal pain (35 %), weight loss (33 %) and, less frequently, with a persistent pancreatic mass. Diabetes mellitus may be the only presenting symptom. In the post-acute phase, pancreatic atrophy and exocrine dysfunction may cause steatorrhea. Gradually aggravated pancreatic insufficiency is the inevitable outcome. The involvement of other organs (bile ducts, salivary glands, kidneys, retroperitoneum) causes extra-pancreatic symptoms, which occasionally appear to be the predominant or even the sole manifestation of the disease. Type 1 AIP (LPSP), presents predominantly with obstructive jaundice in the elderly and responds to steroid therapy. Type 2 AIP (IDCP) seems not to be a systemic disease but a pancreas-specific disorder. It is not associated with either serum IgG4 elevation or with other organ involvement. The presence of extra-pancreatic symptoms, in combination with specific imaging and laboratory findings, contributes to the differential diagnosis between diffuse pancreatic enlargement in AIP and edematous acute pancreatitis. Jaundice, weight loss, abdominal pain and an abrupt onset of diabetes mellitus in the elderly are symptoms presenting in pancreatic cancer as well. Exocrine insufficiency is less common in pancreatic cancer than in AIP, while the presence of marked anorexia, cachexia and narcotic-requiring pain rather establishes the diagnosis of cancer. Nevertheless, for the majority of patients the differential diagnosis between AIP and pancreatic cancer based on clinical manifestations alone is regarded as a very ambitious intention. A representative finding in patients with AIP is the high serum levels of gamma-globulins. Hamano et al first reported in 2001 the correlation between high serum concentration of IgG4 antibodies and AIP, which was not observed in patients with other forms of chronic pancreatitis, pancreatic cancer, primary biliary cirrhosis, primary sclerosing cholangitis and Sjögren syndrome. IgG4 serum levels >135 mg/dL reflected high rates of sensitivity and specificity for AIP diagnosis (95 % and 97 %, respectively). Hirano et al in 2005 obtained comparable results. However, more recently, Ghazale et al have regarded high serum IgG4 concentration as an indication but not diagnostic for AIP. As for the extra-pancreatic lesions of AIP, Kamisawa et al in 2008 reported that in AIP patients with serum IgG4 levels ≥ 220 mg/dL, involvement of other organs was frequent. It is essential to mention at this point that approximately only 1% of all patients with pancreatic cancer have a serum IgG4 level greater than 2-fold the upper limit of normality (50 mg/dL). Mild (<2-fold) elevations of serum IgG4 are seen in up to 10% of subjects without AIP and cannot be used alone for differential diagnosis. It is interesting that while LPSP is associated with elevated titers of autoantibodies, whereas IDCP does not have definitive serological autoimmune biomarkers. This is the reason for debates and concerns regarding use of the term "autoimmune" to describe IDCP. Clinically, these two types have comparable presentations but differ significantly in their demography, serological characteristics, other organ involvement, and relapse rate. Its etiology and pathogenesis are still under investigation, especially during the last decade. Another aspect of interest is the attempt to establish specific criteria for the differential diagnosis between autoimmune pancreatitis and pancreatic cancer, entities that are frequently indistinguishable. An extensive search of the PubMed database was performed with emphasis on articles about the differential diagnosis between autoimmune pancreatitis and pancreatic cancer up to the present. The most interesting outcome of recent research is the theory that autoimmune pancreatitis and its various extra-pancreatic manifestations represent a systemic fibro-inflammatory process called IgG4-related systemic disease. The diagnostic criteria proposed by the Japanese Pancreatic Society, the more expanded HISORT criteria, the new definitions of histological types, and the new guidelines of the International Association of Pancreatology help to establish the diagnosis of the disease types. Thus, the valuable help of the proposed criteria for the differential diagnosis between autoimmune pancreatitis and pancreatic cancer may lead to avoidance of pointless surgical treatments and increased patient morbidity [169].

The levels of serum amylase and lipase are mildly elevated in AIP (approximately 3-fold). The levels of cholestatic enzymes, transaminases and bilirubin are frequently elevated when cholestasis is present because of edema of the head of the pancreas or extra-pancreatic disease with common bile duct involvement.^[15] CA19-9 levels higher than 200 U/mL are rare in AIP, while patients with pancreatic cancer may have significantly higher CA19-9 levels [169].

Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis with a presumed autoimmune etiology. AIP is frequently associated with stenosis of the bile duct in the form of IgG4-related sclerosing cholangitis. One article reviewed recent advances in clinicopathological findings for AIP and IgG4-related sclerosing cholangitis. AIP is currently diagnosed based on characteristic radiological findings (irregular narrowing of the main pancreatic duct and enlargement of the pancreas) in combination with serological findings (elevated serum IgG4 and presence of autoantibodies) and histopathological findings (dense infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis and obliterative phlebitis in the pancreas). Other clinical characteristics include preponderance toward elderly men, common initial symptoms of obstructive jaundice, and favorable response to steroid therapy. Differentiation of AIP from pancreatic cancer is crucial. As AIP is frequently associated with various sclerosing extrapancreatic lesions showing the same peculiar histological findings seen in the pancreas, AIP is currently considered to represent a pancreatic manifestation of IgG4-related sclerosing disease. Considering the age of onset, associated diseases, cholangiography, serum IgG4 levels, and steroid responsiveness, IgG4-related sclerosing cholangitis differs from primary sclerosing cholangitis [177].

Diabetes

The aim of one study was to determine the occurrence and the risk factors of diabetes mellitus (DM) in Chinese patients with chronic pancreatitis (CP), with particular emphasis on those with endoscopic or surgical therapy for CP. Four hundred forty-five contacted CP patients in our hospital between, 1997 and 2007, were followed up. Risk factors for DM were determined in a multivariate analysis after exclusion of 58 patients. The cumulative rate of DM was 52 percent at 20 years after the onset of CP and 28 percent at 10 years after endotherapy or surgery, without significant difference between the 2 therapies. The age at the onset of CP, smoking, chronic pain, and pancreatic calcifications were identified as independent risk factors for developing DM in the patients before any invasive therapy. Smoking and distal pancreatectomy were the independent risk factors for DM development in patients after invasive therapy. It was concluded that the risk of DM seems to be mainly caused by progression of CP because it increased with older age, absence of chronic pain, and pancreatic calcifications, whereas this risk is influenced by smoking and distal pancreatectomy [178].

In Asia

To clarify the clinical and pathophysiological characteristics of autoimmune pancreatitis (AIP) in Asia a retrospective, actual situation survey of AIP diagnosed by Asian criteria was conducted in 10 centers of Japan, Korea, Taiwan, China, and India. A total of 327 AIP cases (258 male and 69 female subjects; average age, 60 years) were enrolled. Obstructive jaundice was the most frequent initial symptom (46-74 %), followed by weight loss (4-51 %) and abdominal pain (19-44 %). Diffuse swelling of the pancreas was frequent in Japan (64 %) and Korea (81 %), but segmental swelling of the pancreas was more frequent in Taiwan (70 %) and China (72 %). Serum immunoglobulin G4 levels were elevated in 58-100 percent of cases in Japan, Korea, and Taiwan. Pathologically, almost all AIPs in Asia were lymphoplasmacytic sclerosing pancreatitis. Sclerosing cholangitis was the most frequent

extrapancreatic lesion (60-81 %). Steroid therapy was a major and effective therapeutic strategy in Japan, Korea, and Taiwan. However, the rate of resection or bypass operation was higher in Taiwan (40 %) and China (72 %) [179].

Morphologic patterns of autoimmune pancreatitis – imaging

To retrospectively evaluate the morphologic characteristics of autoimmune pancreatitis (AIP) using MRI and CT 86 dynamic contrast-enhanced CT and MRI scans in 36 AIP patients were evaluated regarding: different enlargement types, abnormalities of the main pancreatic duct (MPD), morphology of the parenchyma and other associated findings. Three types of enlargement were found:

- a focal type (28 %)
- a diffuse type (involving the entire pancreas (11 %)
- a combined type (56 %)

The MPD was usually dilated together with focal or diffuse narrowing in 67 percent (24/36). Unenhanced MRI showed AIP area in 56 percent (mostly T₁ hypo- and T₂ hyperattenuating), and CT in 10 percent (hypoattenuating). The arterial phase depicted similar patterns for CT and MRI (hypoattenuating in 58 and 52 percent, respectively). Venous and late venous phase patterns were usually hyperattenuating in MRI (65 and 74 %, late enhancement), while CT mostly showed no signal differences (isoattenuating in 57 and 75 %), yielding significant differences between CT and MRI for the venous and the late phase. Miscellaneous findings were: rim sign (25 %), pseudocysts (8 %) and infiltration of large vessels (11 %). It was concluded that “late-enhancement” sign seems to be a key feature and is best detectable with MRI. MRI may be recommended in the diagnostic workup of AIP patients [180].

Computed tomography (CT) may occasionally produce characteristic images of the disease. Two morphological types of AIP are encountered in CT images: typical "diffuse type" and more rare "focal type". The first is characterized by a diffusely enlarged sausage-shaped pancreas and a diffusely irregular and attenuated pancreatic duct. Moreover, a hypodense (capsule-like) rim is visible around the pancreas and is probably due to inflammatory and fibrotic changes in the peripancreatic fat. The focal type of AIP consists of a focal pancreatic mass accompanied by a segmental pancreatic duct stricture and can be hardly distinguished from pancreatic cancer. The lesion appears hypodense on early phase imaging and isodense in the delayed phase, which is a common appearance of cancer as well. The presence of peripancreatic lymphadenopathy, frequent in either AIP or cancer, is another finding that could lead to an erroneous diagnosis. However, distant metastases or infiltration of adjacent tissues is highly indicative of cancer, which is also suggested by post-obstructive dilation of the pancreatic duct. On the other hand, non-metastatic involvement of other organs enhances the suspicion of AIP. For the time being, conventional MRI and PET scan have not been proved to be more efficient than CT either for the diagnosis of AIP or for cancer exclusion. Magnetic resonance elastography, a new technique, which detects wave propagation velocity through the human body, can determine tissue elasticity or stiffness and therefore contribute to the evaluation of pancreatic lesions and exclusion of malignancy [169].

On endoscopic retrograde cholangiopancreatography (ERCP), diffuse irregular narrowing of the main pancreatic duct is rather specific to AIP and is rarely encountered in pancreatic cancer. However, differential diagnosis is difficult in patients with segmental narrowing of the duct. In a recent study, the narrowed portion of the main pancreatic duct was found to be significantly longer in AIP (6.7 ± 3.2 cm) than in cancer cases (2.6 ± 0.8 cm). Furthermore, in

AIP patients with segmental narrowing, post-stenotic dilatation of the distal duct is a rare finding (diameter 2.9 ± 0.7 mm), whereas it is frequent in cancer (diameter 7.1 ± 1.9 mm). Side branches from the narrowed portion are more often visible in AIP than in cancer. Complete obstruction is mainly observed in malignant lesions. On ERCP, stenosis of the lower bile duct may be detected in patients with either AIP or cancer. Brushing cytology of the narrowed portion of the duct plays a significant role in the differential diagnosis. The presence of strictures in the extra-pancreatic portion of the common bile duct or in the hepatic ducts and their branches obviously cannot be associated with cancer, making the diagnosis of AIP more likely. Biopsies taken from a swollen major duodenal papilla (presented in 25 % of AIP cases) show dense lymphoplasmacytic infiltration and fibrosis. Abundant infiltration of the swollen papilla with IgG4-positive plasma cells is specifically detected in AIP cases [169].

Secretin-enhanced MRCP is a method of great diagnostic importance, especially in those cases where ERCP proves unsuccessful. Intravenous administration of secretin increases bile and pancreatic juice secretion and therefore improves the ductal imaging producing better images. The so-called "duct-penetrating sign" which corresponds to a stenotic change of the main pancreatic duct without definite ductal wall irregularity is a highly suggestive sign of AIP [169].

EUS

Endoscopic ultrasonography (EUS) in patients with AIP shows either a diffuse hypoechoic enlargement of the pancreas or a focal irregular hypoechoic mass with or without peripancreatic lymphadenopathy. In the second case the differential diagnosis from cancer is facilitated by the presence of hyperechoic spots within the mass, which may represent compressed pancreatic ducts. Conventional abdominal ultrasonography findings are essentially similar to those of EUS, which, however, is preferable due to its higher resolution and clearer images of the pancreatic parenchyma. EUS-guided fine needle aspiration (EUS-FNA) is very helpful for excluding the possibility of pancreatic cancer, although the small samples make this method insufficient for the diagnosis of AIP. Endoscopic EUS-guided Tru-Cut biopsy provides sufficient tissue and architecture preservation to permit histological diagnosis with low complication rates in experienced hands [169].

EUS-elastography and contrast-enhanced EUS technology have many advantages over conventional EUS. A homogenous stiffness pattern of the lesion in EUS-elastography characterizes the majority of AIP cases. In contrast-enhanced EUS, AIP lesions appear to be homogeneously hypervascular, whereas pancreatic cancer is mainly hypovascular, compared with normal pancreas [169].

MRI/MRCP

To determine and describe the magnetic resonance (MR) imaging-MR cholangiopancreatographic pancreatic and extrapancreatic findings of autoimmune pancreatitis (AIP) and the probability, site, and MR features of recurrent AIP after steroid therapy. This retrospective study was approved by the institutional review board, and the requirement for informed patient consent was waived. The data of 27 patients with AIP were included in the study. All patients had undergone MR imaging with MR cholangiopancreatography before and after steroid treatment and during follow-up (median follow-up period, 45 months). Image analysis included assessment of pancreatic parenchyma enlargement, signal intensity on T1- and T2-weighted MR images, contrast enhancement, and presence of bile duct and/or renal involvement. The probability of AIP recurrence was assessed by using Kaplan-Meier curves and the unadjusted Cox model. At the time of diagnosis, the AIP-affected pancreatic parenchyma showed diffuse enlargement in 14 (52 %) of the 27 patients and segmental enlargement in 13 (48 %). The pancreatic parenchyma appeared hypointense on T1-

weighted images in all 27 (100 %) patients, hyperintense on T2-weighted images in 25 (93 %), and isointense in two (7 %). During the pancreatic phase of the dynamic contrast material-enhanced study, the affected pancreatic parenchyma appeared hypointense in 25 (93 %) patients and isointense in two (7 %). During the portal venous and delayed phases, the images of 19 (70 %) patients showed delayed enhancement. Bile duct involvement was observed in 10 (37 %) patients, and renal involvement was observed in two (7 %). After steroid treatment, six (22 %) patients had recurrent AIP, with a median disease-free interval of 21 months. The sites of recurrence were the pancreas and the kidneys in three of the six patients, solely the pancreas in two patients, and the biliary ducts in one patient. It was concluded that MR imaging with MRCP enables the diagnosis of pancreatic and extrapancreatic AIP and the assessment of changes after steroid therapy [181].

EUS-FNA

Autoimmune pancreatitis (AIP) may mimic pancreatic cancer (PC). The detection of DNA mutations in endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) material may improve discrimination between AIP and PC and is the context for this study. In a retrospective study, archived EUS-FNA material from patients with AIP and PC at two centers was analyzed for *KRAS* mutations and loss-of-heterozygosity analysis involving 18 microsatellite markers. *KRAS* status and the fractional allelic loss (number of affected microsatellites divided by informative ones) were compared for AIP and PC. Thirty-two patients with 33 samples were studied. There were 16 patients with AIP (17 samples) and 16 patients with PC. DNA amplification failed in 7 samples. Of 25 patients (26 samples), 14 had AIP (7 male, age 57 ± 17 years) and 11 had PC (7 male, age 65 ± 14 years). Cytology results for AIP were inflammatory = 3, inconclusive = 10, suspicious for malignancy = 2 and for PC were malignant = 5, suspicious for malignancy = 4 and inconclusive = 2, respectively. *KRAS* mutation was detected in none of the AIP cases and 10/11 PC cases (91 %) or 10/16 PC cases (63 %) accounting for PC cases with failed DNA amplification. Mean fractional allelic loss for the AIP cases (0.16 ± 0.15) was not significantly different from the PC cases (0.26 ± 0.19). It was concluded that *KRAS* mutation in EUS/FNA material from a pancreatic mass is associated with malignancy and may help discriminate from benign conditions such as AIP [182].

Histology

LPSP or AIP without GELs shows 4 characteristic histopathological features:

- dense infiltration of plasma cells and lymphocytes, particularly periductal
- peculiar storiform fibrosis
- venulitis with lymphocytes and plasma cells often leading to obliteration of the affected veins
- abundant (>10 cells per high-power field, HPF) immunoglobulin-IgG4 positive plasma cells IDCP is characterized by GELs, not seen in LPSP.

Intraluminal and intraepithelial neutrophils are present in medium-sized and small ducts as well as in acini, frequently leading to the obliteration and destruction of the lumen. The amount of IgG4-positive plasma cells varies but usually is low (<10 cells/HPF or none). It is unclear whether these subgroups are different stages of the autoimmune process in AIP or represent different diseases. Sah et al in 2010 attempted to accentuate the differences between the two histological subgroups based on 97 patients with AIP. According to this study, patients with LPSP are older than those with IDCP (mean age 62 vs 48 years) have higher serum IgG4 concentrations and are more prone to extrapancreatic manifestations. However, there was no significant difference between the two types regarding the 5-year

survival. The distinction of AIP in two discrete histopathological types was included in the conclusions of the "Honolulu consensus", although there was a vigorous debate about the autoimmune etiology of IDCP, mostly because of the lack of a convincing theory for the granulocyte infiltration and the autoimmune mechanism involved [169]

IgG4-related sclerosing disease

The term IgG4-RSD encompasses a variety of clinical entities once regarded as being entirely separate diseases. The list of organs associated with this condition is growing steadily. Tissue biopsies reveal striking histopathological similarity, regardless of which organ is involved, although subtle differences across organs exist. Diffuse lymphoplasmacytic infiltrates, presence of abundant IgG4-positive plasma cells and extensive fibrosis are the hallmark pathology findings. Tumorous swelling, eosinophilia, and obliterative phlebitis are other frequently observed features. Polyclonal elevations of serum IgG4 are found in most but not all patients. IgG4-RSD is an underrecognized condition about which knowledge is now growing rapidly. Yet there remain many unknowns with regard to its cause, pathogenesis, various clinical presentations, approach to treatment, disease monitoring, and long-term outcomes. A wide variety of organs can be involved in IgG4-RSD. Clinicians should be aware of this entity and consider the diagnosis in the appropriate settings [183].

The spectrum of IgG4-related systemic disease (IgG4-RSD) continues to widen. At most of the sites involved by this condition, the clinical presentation can mimic neoplasm. Pathologic assessment of small biopsies can be critical to proper management. One review summarized the histologic features of IgG4-RSD and the role of immunohistochemistry of IgG4 in the diagnosis. The review period saw further expansion of the list of sites putatively involved by IgG4-RSD, with new, or more detailed, entries related to lung, lymph nodes, stomach, and thyroid. A tentative consensus was reached on the issue of subtypes of autoimmune pancreatitis. The role of immunohistochemistry for IgG4 as an adjunct to the diagnosis of IgG4-RSD was further clarified. Thus, sclerosing lymphoplasmacytic inflammation at almost any site can represent a manifestation of IgG4-RSD. There are several histologic features that can suggest the diagnosis. Immunohistochemistry for IgG4 is a useful diagnostic test to further support the diagnosis [184].

Prompt recognition and management of this disease process in IgG4-related systemic disease are necessary to prevent sclerosis and permanent organ damage. It was reviewed the advances in treatment approaches to IgG4-RSD. Most information regarding treatment is derived from retrospective case series of patients with autoimmune pancreatitis (AIP), and follow-up periods have generally been short. A variety of IgG4-RSD presentations respond rapidly to glucocorticoid treatment. Glucocorticoids have become a standard therapy for AIP, but the indications requiring treatment as well as the appropriate starting dose and duration of therapy remain controversial. The importance of maintenance of glucocorticoids following remission induction is debatable. As our knowledge grows regarding other organ manifestations of IgG4-RSD with longer follow-ups, the necessity of steroid-sparing agents to manage frequent relapses becomes clear. The natural history and long-term prognosis of IgG4-RSD are not well understood. Large prospective studies and randomized controlled trials of patients with wide spectrum manifestations of IgG4-RSD are required to support better approaches to treatment [185].

IgG and IgG4 during follow-up

It is well-known that elevation of IgG and IgG4 is a useful indicator for the diagnosis of autoimmune pancreatitis (AIP), but it is still unknown whether and how they should be

controlled during follow-up, although monitoring them is recommended in Japanese consensus guideline for management of AIP. It was now examined the relation between IgG (IgG4) at initial measurement and IgG (IgG4) at later clinical aggravation. Then, by analyzing relapsed patients in whom IgG and IgG4 were measured at a stable phase more than 3 months before the latest remission induction steroid therapy for the relapse, it was tried to clarify whether the elevation of IgG (IgG4) is observed when clinical relapse occurred. Lastly, IgG (IgG4) at an aggravation phase and IgG (IgG4) after a remission phase were compared. Forty-nine patients (43 men and 6 women) with a diagnosis of AIP based on the Asian diagnostic criteria and who received remission induction therapy with steroid, were included in this study. Average age at onset was 64 years. The average follow-up period after the first remission induction steroid therapy was 52 months (range, 9-134 months). Prednisolone at an initial dosage of 30 to 40 mg/d was administered for 2 to 4 weeks in most cases. It was then tapered gradually until it reached 10 mg/d, and 2.5 to 7.5 mg/d was continued as maintenance therapy in principle. It was defined AIP-related symptomatic unfavorable events requiring steroid as "clinical aggravation." When clinical aggravation occurred after an asymptomatic observation period of more than 3 months without steroid therapy or when it occurred during maintenance steroid therapy, it was called "clinical relapse" in the present study. Clinical relapse was observed in 21 patients (20 men and 1 woman; 43 %) and in 5 of them, more than once. IgG and IgG4 were compared between the patients with (n=17) and without (n=28) a history of clinical relapse to examine whether IgG (IgG4) at initial measurement is related to the later clinical relapse. As for IgG and IgG4, although their decrease shortly after initiating steroid therapy is recognized, significance of their long-term follow-up is still unknown. Judging from the results of the first analysis in this study, however, it seemed difficult to predict later clinical relapse using only IgG or IgG4 at the initial measurement. However, IgG increased significantly at the time of later clinical relapse. On the other hand, such increase was not observed in the patients with very high IgG. It was speculated that they had already been in a state of what is called serological relapse or were sufficiently aggravated serologically, and therefore, there might not have been room for further increase. The transition of IgG4 was similar to that of IgG, but IgG4 seemed to change more remarkably. From the results of the second analysis, it is certain that rising or already high IgG and IgG4 are closely related to clinical relapse, and their careful observation is strongly recommended. Comparing IgG (IgG4) at aggravation and after remission, both decreased significantly after steroid therapy. The decrease of IgG4 was more dynamic than that of IgG in terms of the transition of the IgG4/IgG ratio. This may suggest that IgG4 reflects more precisely the disease activity of AIP. However, interestingly, normalization of IgG4 was less frequent than that of IgG at a remission phase. Especially in the case of IgG4, specificity was inferior. Thus, comparison with the previous value is essential for the evaluation of IgG4. In addition, it may be difficult to compare disease activity between one patient and another on the basis of serum IgG4. In other words, there are greater differences between individuals in IgG4 than in IgG. In conclusion, IgG and IgG4 reflect the disease activity of AIP. By measuring them during follow-up, it may become possible to predict future clinical relapse in a considerable proportion of the patients. Adjusting steroid dose so that elevation of IgG and IgG4 may not occur might be useful for the prevention of clinical relapse [186].

Extra-pancreatic manifestations

Type 1 AIP may affect other organs and tissues (30-50 % of patients) in contrast to type 2, where this is not common. These tissues show similar histological changes, including increased IgG4-positive plasma cell infiltration and response to corticosteroid therapy. The biliary tract is the most commonly (>70 %) involved extra-pancreatic site in patients with AIP and the term "IgG4-associated cholangitis" has replaced the previous term "sclerosing cholangitis". Radiographically, IgG4-associated cholangitis is characterized by bile duct wall

thickening and biliary strictures. Serum IgG4 is usually elevated (a sensitivity of 74 %) and the histological architecture of the lesions is similar to that seen in the pancreas. On ERCP, stenosis of the lower common bile duct may be detected in both AIP and pancreatic cancer, whereas extra-pancreatic stenosis or stenosis of the intrahepatic ducts is indicative of AIP with coexistent IgG4-associated cholangitis. Clinical and radiological findings of IAC may mimic those of primary sclerosing cholangitis. However, the diffuse distribution of primary sclerosing cholangitis with a more frequent involvement of the smaller intrahepatic bile ducts, the "beaded" and "pruned-tree" figure, p-ANCA elevation and the absence of pancreatic disease facilitate the differential diagnosis. Stenosis of the hilar bile duct should also be distinguished from cholangiocarcinoma of the hepatic hilus. The absence of pancreatic lesions and their resolution with steroid therapy are the clues for diagnosis. Lymphoplasmacytic infiltration of the liver in AIP has been reported in several studies, inducing several patterns: portal inflammation with or without interface hepatitis, large bile duct obstruction, portal sclerosis, lobular hepatitis and canalicular cholestasis, which may coexist in the same patient and are described by the term IgG4-hepatopathy. The lymphoplasmacytic type of hepatic inflammatory pseudotumor in the hepatic hilum is regarded as another aspect of liver involvement in AIP patients. The gallbladder is frequently affected in AIP. Diffuse, acalculus, lymphoplasmacytic cholecystitis appears with deep mural and extramural inflammation and is characterized by the same serum and histological findings as in AIP. The salivary and lacrimal glands may also be affected. Kuttner tumor, a chronic sclerosing sialadenitis presenting with asymmetric firm swelling of the submandibular glands, shows marked lymphoplasmacytic infiltration with fibrosis, obliterative phlebitis and destruction of the glandular lobules. These common immunohistochemical characteristics with AIP also reinforce the suggested correlation. Miculicz disease, an idiopathic, bilateral, painless and asymmetric swelling of the lacrimal, parotid and submandibular glands, was previously considered to be a subtype of Sjögren syndrome. However, the histological similarity with AIP, the elevated serum concentration of IgG4 (which is low in Sjögren syndrome) and the absence of anti-SSA or anti-SSB autoantibodies has led to reconsideration of the etiology of this disease. Several cases of retroperitoneal fibrosis associated with AIP have been reported, characterized by lymphoplasmacytic infiltration (lymphoid follicles with germinal centers)¹ IgG4-related periarteritis of the retroperitoneal arteries may coexist with retroperitoneal fibrosis. Akram et al reported that 33 percent of 92 patients with sclerosing mesenteritis had abundant IgG4-positive plasma cell infiltrates in the small bowel mesentery. It seems likely that IgG4-related immunopathologic processes might be involved in the pathogenesis of some cases of sclerosing mesenteritis. Other organs with lesions possibly associated with AIP are the kidney (tubulointerstitial lymphoplasmacytic nephritis), breast (inflammatory pseudotumor), lung (interstitial pneumonia or inflammatory pseudotumor), lymph nodes (Castleman disease-like features, follicular hyperplasia), thyroid (Riedel thyroiditis) and prostate (IgG4-related prostatitis). Type 2 AIP is not usually associated with other organ involvement. However, in 30 percent of reported cases of IDCP inflammatory bowel disease (ulcerative colitis) it is present as well. All the extrapancreatic lesions noted above typically have pathologic features similar to those of type 1 AIP, increased serum level of IgG4 is a common finding, partial or complete resolution following steroid therapy, and may be present despite the absence of pancreatic disease. Thus, a new clinicopathologic concept, called IgG4-related systemic disease has been proposed as a unique autoimmune inflammatory condition in order to include all these lesions [187].

IgG4-associated acute cholecystitis

Autoimmune pancreatitis (AIP) is the pancreatic manifestation of IgG4-associated systemic disease (ISD). Criteria for diagnosis of AIP include recognition of extra-pancreatic organ involvement. Because the diagnosis of AIP can be challenging, even for experts, it is important for clinicians to recognize other target organ damage in this disease. Typical gallbladder findings in AIP have been increasingly recognized. Because cholecystectomy is common in the community, the availability of previous tissue from the gallbladder can provide

an important supportive clue in the diagnosis of AIP. The objective of one review was to examine the literature on common gallbladder pathology findings in AIP, and discuss their clinical utility. Gallbladder involvement in AIP seems to be common. Transmural lymphoplasmacytic inflammatory infiltrates, extramural inflammatory nodules, the presence of tissue eosinophilia, phlebitis, and increased tissue IgG4 are all seen more frequently in the gallbladders of patients with AIP. These findings are not 100 percent specific, because some can be seen in primary sclerosing cholangitis and pancreatic adenocarcinoma. It was concluded that cholecystectomy for the purpose of diagnosing AIP is not recommended. However, if gallbladder specimens from a previous cholecystectomy are available, an expert review of gallbladder slides with IgG4 immunostaining may help to provide additional criteria for diagnosis of autoimmune pancreatitis [188].

IgG4 associated cholangitis

Immunoglobulin G4 associated cholangitis (IAC) is an autoimmune disease associated with autoimmune pancreatitis (AIP). It presents with clinical and radiographic findings similar to primary sclerosing cholangitis (PSC). IAC commonly has a faster, more progressive onset of symptoms and it is more common to see obstructive jaundice in IAC patients compared to those with PSC. One of the hallmarks of IAC is its responsiveness to steroid therapy. Current recommendations for treatment of AIP demonstrate excellent remission of the disease and associated symptoms with initiation of steroid therapy followed by steroid tapering. If untreated, it can progress to irreversible liver failure. One report described a 59 year-old female with undiagnosed IAC who previously had undergone a pancreaticoduodenectomy for a suspected pancreatic cancer and later developed liver failure from presumed PSC. The patient underwent an uncomplicated liver transplantation, but experienced allograft failure within five years due to progressive and irreversible bile duct injury. Radiology and histology suggested recurrence of PSC, but the diagnosis of IAC was suspected based on her past history and confirmed when IgG4 positive cells were found within the intrahepatic bile duct walls on a liver biopsy. A successful liver retransplantation was performed and the patient is currently on triple immunosuppressive therapy [189].

IgG4-associated sialadenitis

An enlarged salivary gland or lacrimal gland raises a wide differential diagnosis that includes both benign inflammatory conditions and malignant disorders. One review aimed to address the numerous controversies that have arisen regarding inflammatory diseases of the salivary gland over the past two centuries and more specifically address the relevance of IgG4 in this setting. A significant percentage of cases previously classified as Mikulicz disease, Küttner tumor, and orbital pseudotumor (idiopathic orbital inflammation) show elevated numbers of IgG4-positive plasma cells, and some of these cases also show elevated levels of serum IgG4. These data support the evolving concept of IgG4-associated sialadenitis/dacroadenitis. The disease presents with enlargement of one or more salivary gland(s) and/or lacrimal gland(s). Histologically this disease is characterized by a dense polyclonal lymphoplasmacytic infiltrate, and is frequently associated with germinal centers, fibrosis and obliterative phlebitis. IgG4-bearing plasma cells are virtually always present, as is an elevated ratio of IgG4 to IgG containing plasma cells. It was summarized that IgG4-related sialadenitis belongs to the IgG4-related systemic disease spectrum and shows a swift response to immunosuppression [190].

IgG4-associated membranous nephropathy

Immunoglobulin G4 (IgG4)-related systemic disease is a rare condition characterized by high levels of circulating IgG4 and IgG4-positive plasma cell infiltrates in various organs, including the pancreas, salivary glands, biliary tract, liver, lung, and kidney. It was described a case of

a 54-year-old man with IgG4-related systemic disease presenting with autoimmune pancreatitis and Mikulicz disease. Steroid therapy decreased circulating IgG4 levels and promoted regression of clinical signs. Thereafter, an increase in serum IgG4 values was followed by the occurrence of nephrotic-range proteinuria. Kidney biopsy showed membranous nephropathy with no IgG4-positive cell infiltrates. A search for circulating immune complexes was negative, and antibodies against M-type phospholipase A(2) receptor could not be detected. Western blot analyses identified circulating IgG3 reacting with superoxide dismutase 2. This case suggests that membranous nephropathy represents an additional renal manifestation of IgG4-related systemic disease, with a pathogenesis possibly associated with neoproduction of autoantibodies targeting podocyte antigen(s) [191].

IgG4-associated pachymeningitis

Hypertrophic pachymeningitis is a rare disease, and the fibrosing inflammatory process causes a thickening of the dura mater. A 62-year-old male undergoing corticosteroid therapy for autoimmune pancreatitis presented with headache and right facial numbness. Brain CT and MRI revealed thickened mass lesion around the tentorium. The specimen obtained by biopsy showed a small number of immunostain areas positive for IgG and IgG4. Systemic IgG4 related disease entity is proposed and analyzed from Japan, and pachymeningitis is also included in the examination. Some autoimmune mechanism is related to pachymeningitis, however, it is necessary to consider well if only the IgG4 has responsibility for the disease [192].

Differential diagnostic criteria

The most significant diagnostic consideration in a patient presenting with obstructive jaundice and a pancreatic mass is pancreatic cancer. AIP may present with the same manifestations and could be an alternative diagnostic. However, usually the diagnosis is not made before surgical treatment is undertaken. Nakazawa et al reported that in 20 percent of AIP cases the diagnosis is made after surgery. Attempting to establish applicable diagnostic guidelines, the Japan Pancreas Society proposed specific criteria for AIP in 2002. Great emphasis was given to the presence of typical imaging findings: diffuse enlargement of the pancreas, diffuse main pancreatic duct narrowing (>1/3 of the length) with an irregular wall (mandatory criteria). Elevated serum autoantibodies, lymphoplasmacytic infiltration and pancreatic fibrosis were characterized as supportive criteria. According to the Japan Pancreas Society, the diagnosis of AIP is established if the mandatory criteria together with at least one of the supportive criteria are present. The more recent Korean criteria and the modified Japanese criteria (2006) also focus mainly on the imaging characteristics of AIP, which are not always helpful, especially in cases of focal disease. The presence of extra-pancreatic lesions was not included in these criteria; this is considered to be another major disadvantage [169].

In 2007, Chari et al proposed expanded diagnostic features, called the "HISORt criteria". According to these, there are five cardinal features of AIP: histology, imaging, serology, other organ involvement and response to therapy. Three diagnostic groups are proposed by the combined HISORt criteria. Group A includes only histological findings which are adequate to establish the diagnosis. Group B requires the presence of characteristic imaging features plus abnormal serology. Finally, Group C includes patients with unexplained pancreatic disease accompanied by abnormal serology, other organ involvement and response to steroid therapy. The HISORt criteria use a wider spectrum of AIP manifestations than the Japanese criteria, reflecting the current understanding of the disease as a systemic steroid-responsive disorder. More recently, following new knowledge, Chari et al at the Honolulu consensus reconsidered the above criteria and distinguished the two histological types of

AIP. Furthermore, Shimosegawa et al announced the guidelines of the International Association of Pancreatology, which included the so far proposed criteria customized into the two discrete subtypes of AIP and further categorized as level 1 or level 2 according to their diagnostic reliability. Specific diagnostic algorithms were proposed based on this new classification. Some key points worth mentioning are [169]:

- type 1 and type 2 AIP seem to be indistinguishable if only imaging and response to steroids are taken into account
- high levels of IgG4 and other organ involvement are indicative for the diagnosis of type 1 AIP
- inflammatory bowel disease is associated mostly with type 2 AIP; a low IgG4 titer and the absence of extra-pancreatic lesions are indicative but not diagnostic for IDCP
- histological confirmation is mandatory in type 2, while in type 1 the other criteria may be sufficient
- patients with atypical histology are now included in a new category called AIP-not otherwise specified.

Based on the above criteria, the diagnosis of AIP can be achieved in most cases. However, especially in the case of focal AIP, the differential diagnosis from pancreatic cancer is not always easy [169].

Treatment

Steroids are regarded as the cornerstone of treatment for AIP, although a few sporadic cases treated with spontaneous resolution have been reported. Prednisone (40 mg daily for 4 weeks, gradually tapered for the next 8 weeks) is the most commonly used regimen. The need for maintaining a low-dose after resolution has been documented either preventively or after relapse. Azathioprine and other immunosuppressive drugs have been tested with encouraging results, but the present data are not sufficient for their use in daily practice. Steroid therapy also has a positive effect in some of the secondary manifestations of the disease, like diabetes mellitus, and in most of the extra-pancreatic lesions. However, it is unclear if it is similarly effective regarding the exocrine function. There is some controversy about the usage of steroids for diagnostic purposes, based on the idea that a response to therapy establishes the diagnosis of AIP. Diagnostic steroid trials should be conducted carefully by pancreatologists only after a negative work-up for cancer including EUS-FNA. It is also worth mentioning that there is a high recurrence rate in type-1 AIP patients after steroid therapy, whereas in type-2 AIP patients relapse is infrequent [169].

Surgery

Despite improved clinical characterization, autoimmune pancreatitis is often still diagnosed only after a major operative procedure. One study seeks to elucidate the circumstances that contribute to an inaccurate preoperative diagnosis. Two independent reviewers identified retrospectively an institutional cohort of 68 patients with adequate clinical data to support the diagnosis of autoimmune pancreatitis. Further data regarding presentation, diagnostic studies, and clinical course was abstracted from medical records. Comparative analyses were performed between those patients who underwent major operative procedures and those who did not. Fifty-three patients underwent operative intervention as their initial treatment. Compared to the 15 patients avoiding operation, these patients were less likely to have diffuse pancreatic enlargement identified on pretreatment imaging (8 % vs 80 %) or to have pretreatment serum IgG4 level evaluations (11 % vs 100 %). Among the 21 patients in whom IgG4 levels were first checked postoperatively, only 12 had increases of at least twice

the upper limit of normal. Pretreatment fine needle aspirates were interpreted incorrectly as definite or suspicious for adenocarcinoma in 12 patients, of whom 10 underwent operation. Clinically important postoperative disease recurrence was suspected or proven in 13 patients. Pitfalls leading to major pancreatic resections in autoimmune pancreatitis include unnecessarily high thresholds for initiating serum IgG4 evaluation, false positive cytologic evaluations for malignancy, and failure to recognize non-classic initial presentations, or recurrence of disease. Better diagnostic strategies are needed, but awareness of these specific findings should help to decrease the number of patients undergoing operation for unrecognized autoimmune pancreatitis [193].

HEREDITARY PANCREATITIS

Idiopathic chronic pancreatitis (ICP) is a complex inflammatory disorder associated with multiple genetic and environmental factors. In individuals without cystic fibrosis (CF), variants of CFTR that inhibit bicarbonate conductance but maintain chloride conductance might selectively impair secretion of pancreatic juice, leading to trypsin activation and pancreatitis. It was investigated whether sequence variants in the gene encoding the pancreatic secretory trypsin inhibitor SPINK1 further increase the risk of pancreatitis in these patients. It was screened patients and controls for variants in SPINK1 associated with risk of chronic pancreatitis and in all 27 exons of CFTR. The final study group included 53 patients with sporadic ICP, 27 probands with familial ICP, 150 unrelated controls, 375 additional controls for limited genotyping. CFTR wild-type and p.R75Q were cloned and expressed in HEK293 cells, and relative conductances of HCO_3^- and Cl^- were measured. SPINK1 variants were identified in 36 percent of subjects and 3 percent of controls (odds ratio 18.1). One variant of CFTR not associated with CF, p.R75Q, was found in 16 percent of subjects and 5.3 percent of controls (odds ratio 3.4). Coinheritance of CFTR p.R75Q and SPINK1 variants occurred in 9 percent of patients and 0.4 percent of controls (odds ratio 25.1). Patch-clamp recordings of cells that expressed CFTR p.R75Q showed normal chloride currents but significantly reduced bicarbonate currents. This means that the CFTR variant p.R75Q causes a selective defect in bicarbonate conductance and increases risk of pancreatitis. Coinheritance of p.R75Q or CF causing CFTR variants with SPINK1 variants significantly increases the risk of ICP [194].

The SPINK1 gene, encoding the human pancreatic secretory trypsin inhibitor, is one of the major genes involved in predisposition to chronic pancreatitis (CP). In one study we have assessed the potential functional impact of 11 SPINK1 promoter variants by means of both luciferase reporter gene assay and electrophoretic mobility shift assay (EMSA), using human pancreatic COLO-357 cells as an expression system. The 11 promoter variants were found to be separable into three distinct categories on the basis of the reporter gene assay results viz loss-of-function, gain-of-function and functionally neutral. These findings, which were validated by EMSA, concurred with data from previous deletion studies and DNase I footprinting assays. Further, binding sites for two transcription factors, HNF1 and PTF1, were newly identified within the SPINK1 promoter by virtue of their being affected by specific variants. Combining the functional data with epidemiological data (derived by resequencing the SPINK1 promoter region in French, German and Indian CP patients and controls), then allowed us to make meaningful inferences as to each variant's likely contribution to CP. It was concluded that only the three promoter variants associated with a loss-of-function (i.e. -53C>T, -142T>C and -147A>G) are likely to be disease-predisposing alterations [195].

OTHER HEREDITARY PANCREATIC DISEASES

Lynch syndrome

Lynch syndrome is caused by germline mutations in MSH2, MLH1, MSH6, and PMS2 mismatch-repair genes and leads to a high risk of colorectal and endometrial cancer. It has previously been shown that constitutional 3' end deletions of EPCAM can cause Lynch syndrome through epigenetic silencing of MSH2 in EPCAM-expressing tissues, resulting in tissue-specific MSH2 deficiency. It was obtained clinical data for 194 carriers of a 3' end EPCAM deletion from 41 families known to us at the Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands and compared cancer risk with data from a previously described cohort of 473 carriers from 91 families with mutations in MLH1, MSH2, MSH6, or a combined EPCAM-MSH2 deletion. Ninety-three of the 194 EPCAM deletion carriers were diagnosed with colorectal cancer; three of the 92 women with EPCAM deletions were diagnosed with endometrial cancer. Carriers of an EPCAM deletion had a 75 percent (95 % confidence interval 65 to 85) cumulative risk of colorectal cancer before the age of 70 years (mean age at diagnosis 43 years), which did not differ significantly from that of carriers of combined EPCAM-MSH2 deletion (69 %) or mutations in MSH2 (77 %) or MLH1 (79 %), but was higher than noted for carriers of MSH6 mutation (50 %). By contrast, women with EPCAM deletions had a 12 percent cumulative risk of endometrial cancer, which was lower than was that noted for carriers of a combined EPCAM-MSH2 deletion (55 %) or of a mutation in MSH2 (51 %) or MSH6 (34 %), but did not differ significantly from that noted for MLH1 (33 %) mutation carriers. This risk seems to be restricted to deletions that extend close to the MSH2 gene promoter. Of 194 carriers of an EPCAM deletion, three had duodenal cancer and four had pancreatic cancer. It was concluded that EPCAM deletion carriers have a high risk of colorectal cancer; only those with deletions extending close to the MSH2 promoter have an increased risk of endometrial cancer. These results underscore the effect of mosaic MSH2 deficiency, leading to variable cancer risks, and could form the basis of an optimised protocol for the recognition and targeted prevention of cancer in EPCAM deletion carriers [196].

Carney complex

Carney complex (CNC) is a rare disease inherited as an autosomal dominant trait, associated with various tumors, and caused most frequently by inactivation of the PRKAR1A gene. In a recent investigation of a large cohort of CNC patients, it was identified several cases of pancreatic neoplasms. This possible association and PRKAR1A's possible involvement in pancreatic tumor have not been reported previously. Nine patients (2.5 %) with CNC and pancreatic neoplasms in an international cohort of 354 CNC patients were identified; it was studied six of them. Immunohistochemistry and PRKAR1A sequencing were obtained. Three men and three women with a mean age of 49 years (range 34-75 yr) had acinar cell carcinoma (n=2), adenocarcinoma (n=1), and intraductal pancreatic mucinous neoplasm (n=3). Five patients had a germline PRKAR1A mutation, including two patients with acinar cell carcinoma, for whom mutations were found in a hemizygous state in the tumor, suggesting loss of heterozygosity. PRKAR1A expression was not detected in five of the six pancreatic neoplasms from CNC patients, whereas the protein was amply expressed on other sporadic pancreatic tumors and normal tissue. It was concluded that an unexpectedly high prevalence of rare pancreatic tumors was found among CNC patients. Immunohistochemistry and loss-of-heterozygosity studies suggest that PRKAR1A could function as a tumor suppressor gene in pancreatic tissue, at least in the context of CNC. Clinicians taking care of CNC patients should be aware of the possible association of CNC with a potentially aggressive pancreatic neoplasm [197].

Pearson syndrome

Pearson syndrome is a multisystem disease including refractory anemia, vacuolization of marrow precursors and pancreatic fibrosis. The disease starts during infancy and affects various tissues and organs, and most affected children die before the age of 3 years. Pearson syndrome is caused by de novo large-scale deletions or, more rarely, duplications in the mitochondrial genome. In one report, it was described a Pearson syndrome patient harboring multiple mitochondrial deletions which is the first case described and studied in Tunisia. In fact, we reported the common 4.977kb deletion and two novel heteroplasmic deletions (5.030 and 5.234kb) of the mtDNA. These deletions affect several protein-coding and tRNAs genes and could strongly lead to defects in mitochondrial polypeptides synthesis, and impair oxidative phosphorylation and energy metabolism in the respiratory chain in the studied patient [198].

PANCREATIC STELLATE CELLS

Pancreatic stellate cells (PSCs) are important players in pancreatic fibrosis and are major contributors to the extracellular matrix proteins observed with the stromal response characteristic of pancreatic ductal adenocarcinoma (PDAC). Pancreatic stellate cells are also believed to secrete soluble factors that promote tumor progression; however, no comprehensive analysis of the PSC proteome in either the quiescent or the activated state has been reported. Using 2-dimensional tandem mass spectrometry and the RLT-PSC cell line, it was presented a comprehensive study describing and comparing the quiescent and activated human PSC-secreted proteomes. Very few proteins are secreted in the quiescent state. In stark contrast, activated PSCs secreted a vast array of proteins. Many of these proteins differed from those secreted by PDAC-derived cell lines. Proteins associated with wound healing, proliferation, apoptosis, fibrosis, and invasion were characterized. Selected proteins were verified in human tissue samples from PDAC, dysplastic pancreas, and normal pancreas using Western blot analysis and immunohistochemical staining. These findings lay the foundation for characterizing PSC-derived proteins involved in stroma-tumor interactions and the promotion of pancreatitis and PDAC [199].

CYSTIC FIBROSIS

Postprandial hyperglycemia is an important clinical problem in cystic fibrosis (CF), but the contribution of fat malabsorption, rapid gastric emptying, and the incretin axis has not been widely considered. The aim of one study was to evaluate these aspects of gut function in nondiabetic CF patients. It was conducted a randomized, double-blind, placebo-controlled crossover study at a clinical research laboratory. Five nondiabetic CF patients (three males; age, 26 ± 1 year; body mass index, 20 ± 1 kg/m² with exocrine pancreatic insufficiency and six healthy subjects of similar age and body mass index participated in the study. The CF patients consumed a radiolabeled mashed potato meal on 2 separate days, together with four capsules of Creon Forte (100,000 IU lipase) or placebo. Healthy subjects consumed the meal once, without pancreatic enzymes. Gastric emptying was measured using scintigraphy, and blood was sampled frequently for blood glucose and plasma glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon concentrations. CF patients had significantly more rapid gastric emptying, impaired secretion of GLP-1 and GIP, and greater postprandial glycemic excursions than healthy subjects. Pancreatic enzyme supplementation normalized gastric emptying and GLP-1 secretion and tended to increase glucagon, but did not completely restore GIP secretion or normalize postprandial blood glucose. There was an excellent correlation between gastric emptying and blood glucose concentration at 60 min. It was concluded that pancreatic enzyme supplementation plays an

important role in incretin secretion, gastric emptying, and postprandial hyperglycemia in CF [200].

Different mutations in the cystic fibrosis gene (CFTR) are associated with different functional status of the exocrine pancreas. It was investigated whether CFTR genotypes determine the risk of pancreatitis in patients with cystic fibrosis (CF). Patients with pancreatic-sufficient CF were identified from two CF population-based databases (n=277; 62 with pancreatitis and 215 without pancreatitis); patients' genotypes and clinical characteristics were analyzed. The loss of pancreatic function associated with each CFTR genotype was determined based on the pancreatic insufficiency prevalence (PIP) score. Patients with pancreatitis were more likely to have genotypes associated with mild (70 %) than moderate-severe (30 %) PIP scores. The cumulative proportion of patients who developed pancreatitis through to the age of 50 years was significantly greater for genotypes associated with mild (50 %) than moderate-severe (27 %) PIP scores. The genotype associated with mild PIP scores had a hazard ratio of 2.4 for pancreatitis (95 % confidence interval, 1.3 to 4.5). Patients with pancreatitis were diagnosed with CF at a significant older median age than those without pancreatitis (15 years vs 9 years and had lower mean levels of sweat chloride than patients without pancreatitis. Specific CFTR genotypes are significantly associated with pancreatitis. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than patients with genotypes associated with moderate-severe phenotypes. This observation provides further insight into the complex pathogenesis of pancreatitis [201].

PANCREAS DIVISUM

Pancreas divisum, the most common congenital pancreatic anomaly, is associated with three main duct abnormalities: type I, with total failure of fusion; type II, with dorsal duct dominant drainage; and type III, incomplete divisum where a small communication branch is present. Three clinical conditions are associated with pancreas divisum:

- acute recurrent pancreatitis
- chronic pancreatitis with the chronic inflammation in the dorsal bed
- abdominal "pancreatic-type" obstructive pain.

Endoscopic retrograde cholangiopancreatography is the primary method for diagnosing pancreas divisum, but magnetic resonance cholangiopancreatography is becoming a first choice for non-invasive evaluation. Pancreas divisum per se does not require medical intervention. Patients who experience mild episodic acute pancreatitis should be managed medically. Surgical or endoscopic interventions relieve the obstruction by improving dorsal duct drainage via the minor papilla [202].

Pancreas divisum (PD) is the most common congenital variation of pancreatic duct anatomy, arising when the embryological ventral and dorsal endodermal buds fail to fuse ("classic" PD) or only partially fuse ("incomplete" PD). With this ductal variant, pancreatic drainage is mainly through the accessory papilla. The possibility that PD has pathophysiological consequences related to idiopathic pancreatitis (IP) emerged in the 1970s, when endoscopists identified PD by endoscopic retrograde cholangiopancreatography (ERCP) in patients. For more than 150 years, anatomists and later clinicians used different methods to describe PD, including autopsy, surgery, endoscopic retrograde pancreatography (ERCP), magnetic resonance pancreatography (MRCP), and secretin-MRCP (S-MRCP). The aim of more than 90 percent of autopsy studies was to classify normal variations of human pancreatic ducts and structures, whereas the aim of ERCP studies was to determine the relationship between PD and IP. Accumulating data indicate that the prevalence of PD is no greater in IP compared to

the general population. Initially, investigators using ERCP reported a greater prevalence of PD in IP compared to the general population. These data later were contradicted by other ERCP studies. Multiple factors might account for these differences; the early studies might have been biased by referral pattern, patient selection, and inclusion of subjects with poorly characterized pancreatic In an autopsy and MRCP studies, the prevalence of PD in the general population was about 8 percent. In the ERCP studies, however, the prevalence of PD was about 4 percent in the general population and about 8 percent in patients with IP. These data support the conclusion that in ERCP studies, the prevalence of PD in the general population is because of under recognition and/or referral bias, and that there is no association between PD and IP. DiMagno and DiMagno analyzed data from 41 endoscopic studies and reported that up to 53 percent of patients had evidence of CP. More recently, a systematic review of ERCP detection rates for pancreas divisum included 17 studies: six from Asia, three from Europe, and eight from the United States. Overall, endoscopists detected PD in 2.9 percent of ERCPs (899 of 31413), but prevalence varied significantly by geographic location: 1.5 percent (317 of 21636 ERCPs) in Asia, significantly lower than 5.7 percent (395 of 6578; $P < 0.001$) in the United States and 6.0 percent (899 of 31413) for Europe. Perhaps the most interesting observation by Liao et al is that the prevalence of PD appears to vary by different geographic locations. These regional differences, however, are likely attributable to the degree that endoscopists search for PD (by examining both ductal systems) or to referral bias or other factors as discussed previously. Currently, it remains controversial whether PD causes IP and whether surgical or endoscopic drainage procedures of the duct of Santorini reduce pain and attacks of pancreatitis. Authors use different terminology to describe "recurrent pancreatitis." The most commonly used term is idiopathic recurrent acute pancreatitis (IRAP), which sidesteps the consideration that IRAP patients have chronic pancreatitis (CP) from the initial presentation of symptoms. The initial presentation of patients with early-onset idiopathic CP is pain, followed by recurrent attacks of pain at variable intervals of months to years, and many years later the hallmark features of CP (calcification, diabetes, and malabsorption) occur. Many patients with PD and IRAP have CP. The term recurrent acute pancreatitis (RAP) may describe all patients with this condition, regardless of etiology, most of whom have identifiable causes of RAP (e.g. biliary lithiasis, hypertriglyceridemia, hypercalcemia). The term idiopathic RAP (IRAP) indicates patients who have no identifiable cause of RAP, who, in our opinion, have early idiopathic CP. Data are insufficient, however, to completely exclude the possibility that, in some patients, PD combines with CFTR mutations as a "two-hit" phenomenon that increases the susceptibility to IP. More than one third of patients with pancreatitis or presumed pancreaticobiliary pain respond to placebo. Predicting endoscopic or surgical response is not standardized. In uncontrolled studies, authors report a significant symptomatic response to surgery and endotherapy in IP patients with PD, but the response is largely limited to IRAP and not idiopathic CP or chronic pain. Endoscopic therapy of patients with IP and PD without evidence of CP remains unproven. This controversy can be settled by randomized controlled trials of endoscopic therapy versus sham intervention with long-term follow-up [158].

FAMILIAL PANCREATIC CANCER

Pancreatic cancer is recognized as having a strong hereditary component. The term "familial pancreatic cancer" (FPC) describes families in which two or more first-degree relatives have been diagnosed with pancreatic cancer. Past studies demonstrate significantly heightened risk among family members from such kindreds, with the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins University noting observed-to-expected pancreatic cancer risk of 4.6 for kindreds with one affected relative, 6.4 for those with two affected relatives, and 32.0 for those with three relatives affected with pancreatic cancer. More recent data from the NFPTR suggest that the risk of developing pancreatic cancer is 6.9 in an individual with one first-degree relative and 4.0 in an individual with two first-degree relatives,

whereas family members with three or more affected first-degree relatives have a 17.0-fold risk for developing pancreatic cancer when compared to what is expected from Surveillance Epidemiology and End Results (SEER) data. A recent study prospectively investigated the relationship between pancreatic cancer mortality and a family history of pancreatic and other cancers in a study of about 1.1 million men and women who took part in the Cancer Prevention Study II. Between enrollment in 1982 and 2006, 7306 pancreatic cancer deaths were reported; a family history of pancreatic cancer in a sibling or parent was associated significantly with pancreatic cancer mortality (adjusted RR 1.66; 95 % confidence interval 1.43 to 1.94) and was greater among participants who were less than 60 years of age (adjusted RR 2.89; 95 % confidence interval 1.67 to 5.02). Weaker, but still significant, associations with pancreatic cancer risk were also observed for a history of stomach, liver, or colon cancer among a sibling or parent. Shared risk factors, such as *H. pylori* infection for stomach and pancreatic cancer and cigarette smoking for colon and pancreatic cancer, may play an etiologic role in these neoplastic processes [203].

PALB2

Mutations in the BRCA tumor suppressor genes may account for a percentage of FPC cases. The known breast cancer gene PALB2 has also been identified as a pancreatic adenocarcinoma susceptibility gene. PALB2 acts as a bridge between BRCA2 and BRCA1 as part of a complex that is crucial for double-strand break repair and homologous recombination. PALB2 directly binds BRCA1 and functions as the molecular scaffold in the formation of the BRCA1-PALB2-BRCA2 complex. A history of breast cancer was noted for all three families carrying a PALB2 mutation [203].

CDKN2A

Germline mutations in CDKN2A have been reported in pancreatic cancer families, but genetic counseling for pancreatic cancer risk has been limited by lack of information on CDKN2A mutation carriers outside of selected pancreatic or melanoma kindreds. Lymphocyte DNA from consecutive, unselected white non-Hispanic patients with pancreatic adenocarcinoma was used to sequence CDKN2A. Frequencies of mutations that alter the coding of p16INK4 or p14ARF were quantified overall and in subgroups. Penetrance and likelihood of carrying mutations by family history were estimated. Among 1537 cases, 9 (0.6 %) carried germline mutations in CDKN2A, including three previously unreported mutations. CDKN2A mutation carriers were more likely to have a family history of pancreatic cancer or melanoma, and a personal history of melanoma. Among cases who reported having a first-degree relative with pancreatic cancer or melanoma, the carrier proportions were 3.3 and 5.3 percent, respectively. Penetrance for mutation carriers by age 80 was calculated to be 58 percent for pancreatic cancer (95 % confidence interval 8 to 86 %), and 39 percent for melanoma (95 % confidence interval 0 to 80 %). Among cases who ever smoked cigarettes, the risk for pancreatic cancer was higher for carriers compared with non-carriers (HR 25.8), but among nonsmokers, this comparison did not reach statistical significance. Germline mutations in CDKN2A among unselected pancreatic cancer patients are uncommon, although notably penetrant, especially among smokers. Carriers of germline mutations of CDKN2A should be counseled to avoid tobacco use to decrease risk of pancreatic cancer in addition to taking measures to decrease melanoma risk [204].

PANCREATIC CANCER, GENERAL ASPECTS

The directions of differentiation and the molecular features of ductal pancreatic cancer have by now been explored in reasonable detail. Already, diagnoses and therapeutic strategies benefit from observations distinguishing the major variant types of pancreatic cancer and the differing stages of disease at presentation. Additionally, individual patients differ within each variant type. In certain high-risk groups, this permits focused screening efforts. The tumorigenic influences that characterize individual patients are increasingly considered appropriate in defining clinical treatment plans. As a result, multiple variables affect success when individualizing screening or therapy. These competing variables often limit the potential for success: some variables dominate and should receive greater consideration than others. Simplistic expectations, often falsely optimistic, for individualized care may fail to “pan out” in the real world. The development of individualized care will be efficient only when the full complexity of the disease is embraced [205].

Guidelines

The level of scientific evidence on which the National Comprehensive Cancer Network (NCCN) guidelines are based has not been systematically investigated. We describe the distribution of categories of evidence and consensus (EC) among the 10 most common cancers with regard to recommendations for staging, initial and salvage therapy, and surveillance. NCCN uses a system of guideline development distinct from other major professional organizations. The NCCN definitions for EC are as follows: category I, high level of evidence with uniform consensus; category IIA, lower level of evidence with uniform consensus; category IIB, lower level of evidence without a uniform consensus but with no major disagreement; and category III, any level of evidence but with major disagreement. Of the 1,023 recommendations found in the 10 guidelines, the proportions of category I, IIA, IIB, and III EC were 6 percent, 83 percent, 10 percent, and 1 percent, respectively. Recommendations with category I EC were found in kidney (20 %), breast (19 %), lung (6 %), pancreatic (6 %), non-Hodgkin's lymphoma (6 %), melanoma (6 %), prostate (4 %), and colorectal (1 %) guidelines. Urinary bladder and uterine guidelines did not have any category I recommendations. Eight percent of all therapeutic recommendations were category I. Guidelines with the highest proportions of category I therapeutic recommendations were for breast (30 %) and kidney (28 %) cancers. No category I recommendations were found on screening or surveillance. It was concluded that the recommendations issued in the NCCN guidelines are largely developed from lower levels of evidence but with uniform expert opinion. This underscores the urgent need and available opportunities to expand evidence base in oncology [206].

New guidelines were written for pancreatic cancer by the Japan Pancreas Society. The guidelines showed algorithms for the diagnosis and treatment of pancreatic cancer, address five subjects: diagnosis, chemotherapy, radiation therapy, surgical therapy and adjuvant therapy, and include 25 clinical questions (CQs) and 39 recommendations. There are five degrees of recommendation [207]:

- A Strongly recommended because there is strong scientific evidence.
- B Recommended because there is scientific evidence.
- C1 Recommended although there is no scientific evidence.
- C2 Not recommended because there is no scientific evidence.
- D Not recommended because there is evidence showing that it is ineffective or harmful.

Diagnosis

CQ1-1 What are risk factors for pancreatic cancer?

The below-mentioned risk factors have been reported to have evidences supporting the relationship between the factors and pancreatic cancer:

- Family history: pancreatic cancer and hereditary pancreatic cancer syndrome.
- Accompanying diseases: diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm (IPMN).
- Habits: tobacco.

RECOMMENDATION 1-1

- Patients with more than one risk factor are recommended to undergo further examination to detect pancreatic cancer (Grade B).
- IPMN progresses to invasive cancer and accompanies pancreatic cancer. IPMN should be adequately assessed and carefully followed up (Grade B).

CQ1-2 What are the clinical symptoms of pancreatic cancer?

The below-mentioned clinical symptoms have been reported as those of pancreatic cancer:

- Abdominal pain is the most frequent symptom, followed by jaundice, back pain and body weight loss.
- Clinically silent pancreatic cancer.
- Fifty percent of pancreatic cancer patients show early-onset diabetes mellitus (glycogen metabolism disturbance) within 3 years.

RECOMMENDATION 1-2

- Patients with unexplainable abdominal pain, back pain, jaundice and/or body weight loss should undergo further examination for pancreatic cancer. However, the clinical outcome of symptomatic pancreatic cancer is poor (Grade B).
- Early-onset diabetes mellitus (poor glycogen metabolism) and deterioration of diabetes mellitus suggest the presence of pancreatic cancer and necessitate further examination for pancreatic cancer (Grade B). Early-onset diabetes mellitus (within less than 3 years) may indicate pancreatic cancer.

CQ1-3 What is the first step when pancreatic cancer is suspected?

The below-mentioned examinations are the first-step diagnostic procedures of pancreatic cancer:

- Serum pancreatic enzyme
- Tumor markers
- Ultrasound (US)
- Computed tomography (CT).

RECOMMENDATION 1-3

- The serum pancreatic enzyme level is important, but is not specific for pancreatic cancer (Grade C1).
- Serum tumor makers including CA19-9 are recommended for the diagnosis of pancreatic cancer and follow-up of pancreatic cancer (Grade B), but they are not useful for the diagnosis of early pancreatic cancer.
- US is recommended for the first screening for pancreatic cancer (Grade B) but has a low rate of detecting pancreatic cancer (Grade C1). Dilatation of the main pancreatic duct or a pancreatic cyst is an important indirect sign of pancreatic cancer (Grade B). Further examination, including CT, is therefore strongly recommended if such signs are evident (Grade A).
- Patients the abnormal findings listed above should be periodically examined and careful follow-up is recommended if no diagnosis of pancreatic cancer obtained (Grade B).

CQ1-4 What is the second step when pancreatic cancer is suspected?

RECOMMENDATION 1-4

- Qualitative diagnosis is important and is strongly recommended to determine the treatment of pancreatic cancer (Grade A).
- US and CT (enhancing) should be performed and additional examination by magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), ERP or positron emission tomography is strongly recommended when necessary (Grade A).

CQ1-5 What is the significance and indications for cytology and biopsy of pancreatic cancer?

RECOMMENDATION 1-5

- Either a histological or cytological diagnosis is recommended before treatment started if no qualitative diagnosis of pancreatic mass obtained. Aspiration cytology or histology with US guidance, cytology or histology under endoscopic ultrasonography, pancreatic juice cytology under endoscopic retrograde cholangiopancreatography (ERCP) or histology under ERCP should be obtained to achieve a definite diagnosis, depending on the patients or institution (Grade B).
- Aspiration cytology under endoscopic ultrasonography is useful when the lesion is not detected by ultrasonography or CT (Grade C1).
- A genetic analysis is important to confirm the cytology or histology (Grade C1).

CQ1-6 How do you determine clinical staging of pancreatic cancer?

RECOMMENDATION 1-6

- Multidetector CT or EUS is recommended for staging diagnosis (TNM) of pancreatic cancer (Grade B).

Chemotherapy

CQ2-1 Is chemotherapy alone recommended for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 2-1

- Chemotherapy alone is recommended as one of options for the treatment of locally advanced unresectable pancreatic cancer (Grade B).

CQ2-2 What is the first-line chemotherapy for metastatic pancreatic cancer?

RECOMMENDATION 2-2

- Gemcitabine (GEM) is recommended as the first-line treatment for metastatic pancreatic cancer (Grade A).

CQ2-3 How long is GEM continued for unresectable pancreatic cancer?

RECOMMENDATION 2-3

- GEM is continuously administered for unresectable pancreatic cancer until clear progression becomes evident if there are no adverse effects causing interruption of the administration of GEM (Grade B).

CQ2-4 Is second-line chemotherapy recommended for unresectable pancreatic cancer?

RECOMMENDATION 2-4

- There is no scientific evidence of effective second-line chemotherapy within the insurance allowance in this country, but some reports suggest effectiveness. Some recent randomized clinical trials in other countries have reported effective second-line chemotherapy. Second-line chemotherapy can be considered in patients whose physical status is good and are fully informed after a detailed explanation (Grade C1).

Radiotherapy

CQ3-1 Is chemoradiation effective for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-1

- Chemoradiation is effective for locally advanced unresectable pancreatic cancer and is recommended as one of the options for treatment (Grade B).

CQ3-2 What is the standard combined chemotherapy for chemoradiation for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-2

- 5-fluorouracil (5-FU) (Grade B) is the standard chemotherapy for chemoradiation for locally advanced pancreatic cancer. Although there is no definite evidence supporting GEM-based chemoradiation, some report its usefulness. A safe regimen of GEM-based chemoradiation can be considered as one of the options for treatment after the procedure is fully explained and the patient provides informed consent (Grade C1).

CQ3-3 Is the lymph node included in the clinical standard field of external radiation therapy for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-3

- There have been no prospective randomized clinical trials concerning this question. Radiation including the tumor and the positive lymph nodes in the radiation field is recommended prophylactically, although there is no supportive scientific evidence (Grade C1).

CQ3-4 Is intraoperative radiation effective for locally advanced pancreatic cancer?

RECOMMENDATION 3-4

- There are reports of the efficacy of intraoperative radiation for locally advanced unresectable pancreatic cancer. However, there is no scientific evidence that intraoperative radiation improves the clinical course of locally advanced unresectable pancreatic cancer (Grade C1).

CQ3-5 Does chemoradiation improve the quality of life of patients with unresectable pancreatic cancer?

RECOMMENDATION 3-5

- Cancer radiation therapy (Grade C1) and chemotherapy (Grade B) are therefore recommended to improve the quality of patients with unresectable pancreatic cancer.

Surgical therapy

CQ4-1 Is surgical resection useful for Stage IVa pancreatic cancer?

RECOMMENDATION 4-1

- Surgical resection with an intended curative resection is recommended for pancreatic cancer up to Stage IVa (Grade B). Stage IVa: Stage IVa indicates (S2 or R2 or PV2) and (N0 or N1) by Japan Pancreas Society Classification of pancreatic cancer, 4th Edition.

CQ4-2 Is preservation of the stomach useful in pancreatoduodenectomy for pancreatic head cancer?

RECOMMENDATION 4-2

It is not clear whether preservation of the stomach improves the rate of post-operative complications, quality of life, postoperative pancreatic function and nutrition status of patients with pancreatic cancer or not (Grade C1). Preservation of the stomach decreases the operation time and blood loss in pancreatoduodenectomy but does not decrease the survival rate after a surgical resection (Grade C1).

CQ4-3 Does combined portal vein resection improve the clinical outcome of patients with pancreatic head cancer?

RECOMMENDATION 4-3

The effect of prophylactic portal vein resection intended to increase the curability on the clinical course of patients with pancreatic cancer is unclear. A portal vein resection is indicated when surgical and dissection margins can be free from cancer cells by portal vein resection (Grade C1).

CQ4-4 Is a radical resection with extended lymph node dissection useful for pancreatic cancer?

RECOMMENDATION 4-4

The contribution of extended lymph node and nerve plexus dissection to the improvement of clinical course of patients with pancreatic cancer is unclear and there is no evidence to support the performance of such an extended radical resection (Grade C2).

CQ4-5 Is the incidence of complications after pancreas resection low in a high volume center?

RECOMMENDATION 4-5

The incidence of complications tends to be low in pancreatic surgery including pancreatoduodenectomy and the management of complications tends to be superior in institutions with a high volume of pancreatic surgery (Grade B).

CQ4-6 Is surgical bypass or biliary stent significant in unresectable pancreatic cancer?

RECOMMENDATION 4-6

Hepaticojejunostomy for the obstructive jaundice and prophylactic gastrojejunostomy is recommended in patients with unresectable obstructive jaundice after laparotomy (Grade B).

Adjuvant therapy

CQ5-1 Does pre-operative therapy improve the clinical outcome of patients with pancreatic cancer?

RECOMMENDATION 5-1

There is increasing evidence supporting the efficacy of preoperative treatment [chemoradiation and chemotherapy]. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-2 Is intraoperative radiation therapy recommended at the time of resection of pancreatic cancer?

RECOMMENDATION 5-2

There has been no definite evidence supporting the usefulness of intraoperative radiotherapy. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-3 Is post-operative chemoradiation recommended for pancreatic cancer?

RECOMMENDATION 5-3

Meta-analysis of 5-FU-based post-operative chemoradiation revealed no supportive evidence. However, clinical trials or analyses of the long term are required to determine whether GEM-based post-operative chemoradiation improves the clinical outcome (Grade C1).

CQ5-4 Is post-operative adjuvant therapy recommended for pancreatic cancer?

RECOMMENDATION 5-4

There is no definite international consensus on post-operative adjuvant therapy. Post-operative GEM is safe and effective and is recommended as post-operative chemotherapy (Grade B).

Prophylaxis

Treatment with daily aspirin for 5 years or longer reduces subsequent risk of colorectal cancer. Several lines of evidence suggest that aspirin might also reduce risk of other cancers, particularly of the gastrointestinal tract, but proof in man is lacking. It was studied deaths due to cancer during and after randomised trials of daily aspirin versus control done originally for prevention of vascular events. It was used individual patient data from all randomised trials of daily aspirin versus no aspirin with mean duration of scheduled trial treatment of 4 years or longer to determine the effect of allocation to aspirin on risk of cancer death in relation to scheduled duration of trial treatment for gastrointestinal and non-gastrointestinal cancers. In three large UK trials, long-term post-trial follow-up of individual patients was obtained from death certificates and cancer registries. In eight eligible trials

(25 570 patients, 674 cancer deaths), allocation to aspirin reduced death due to cancer (pooled odds ratio 0.79, 95 % confidence interval 0.68 to 0.92). On analysis of individual patient data, which were available from seven trials (23 535 patients, 657 cancer deaths), benefit was apparent only after 5 years' follow-up (all cancers, hazard ratio 0.66; gastrointestinal cancers, 0.46). The 20-year risk of cancer death (1634 deaths in 12 659 patients in three trials) remained lower in the aspirin groups than in the control groups (all solid cancers, HR 0.80; gastrointestinal cancers, 0.65), and benefit increased with scheduled duration of trial treatment (≥ 7.5 years: all solid cancers, 0.69; gastrointestinal cancers, 0.41). The latent period before an effect on deaths was about 5 years for oesophageal, pancreatic, brain, and lung cancer, but was more delayed for stomach, colorectal, and prostate cancer. For lung and oesophageal cancer, benefit was confined to adenocarcinomas, and the overall effect on 20-year risk of cancer death was greatest for adenocarcinomas (HR 0.66). Benefit was unrelated to aspirin dose (75 mg upwards), gender, or smoking, but increased with age—the absolute reduction in 20-year risk of cancer death reaching 7 percent at age 65 years and older. Thus, daily aspirin reduced deaths due to several common cancers during and after the trials. Benefit increased with duration of treatment and was consistent across the different study populations. These findings have implications for guidelines on use of aspirin and for understanding of carcinogenesis and its susceptibility to drug intervention [208].

Statins

The aim of one study was to investigate whether the use of statins was associated with pancreatic cancer risk. It was conducted a population-based case-control study in Taiwan. Data were retrospectively collected from the Taiwan National health Insurance Research Database. Cases consisted of all patients who were 50 years or older and had a first-time diagnosis of pancreatic cancer for the period between 2003 and 2008. The control subjects were matched to cases by age, gender, and index date. Adjusted odds ratios (ORs) and 95 % confidence intervals were estimated by using multiple logistic regression. It was examined 190 pancreatic cancer cases and 760 control subjects. The unadjusted OR for any statin prescription was 1.07 (95 % confidence interval 0.72 to 2.06), and the adjusted OR was 0.87 (95 % confidence interval 0.56 to 1.36). Compared with no use of statins, the adjusted ORs were 1.06 (95 % confidence interval 0.61 to 1.85) for the group having been prescribed statins with cumulative defined daily doses less than 114 and 0.71 (95 % confidence interval 0.39 to 1.30) for the group with cumulative statin use of 114 defined daily doses or more. Thus, the study does not provide support for a beneficial association between usage of statin and pancreatic cancer [209].

Histopathology

Pancreatic intraepithelial neoplasia (PanIN) has been found in association with pancreatic ductal adenocarcinoma, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystic neoplasm, and other pancreatic lesions, but the characteristics of PanINs associated with these lesions are not well characterized. In one study, 185 partial or total pancreatectomy specimens were collected, and 173 had complete slides for reviewed, which included 74 pancreatic ductal adenocarcinomas, 28 IPMNs, 7 mucinous cystic neoplasms, 44 other nonductal tumors, and 20 nontumorous lesions. Differences in grade, extent, and duct involvement among PanINs associated with different lesions were analyzed. Patients with PanINs were older than those without, regardless of associated tumor or lesions. No gender predilection was noted. PanINs were found in 89, 96, 86, 64, and 55 percent pancreata with ductal adenocarcinomas, IPMNs, mucinous cystic neoplasm, other nonductal tumors, and nontumorous lesions, respectively. PanIN 1 and 2 were commonly associated with all types of lesions, but high-grade PanIN 3 was more frequently associated with ductal adenocarcinomas. Ductal involvement of PanINs was more extensive in association with

ductal adenocarcinomas than in any other types of pancreatic tumors or lesions. PanINs associated with pancreatic ductal adenocarcinomas affected both the main and branched ducts, whereas PanINs associated with other types of pancreatic tumors or lesions were mainly present in the branch ducts. No statistical differences were observed in distribution, extent, and grade of PanINs among IPMNs, mucinous cystic neoplasms, other nonductal tumors, and nontumorous lesions. Our study demonstrated a high concurrence between PanINs and other precancerous lesions and histologic features of PanINs associated with different pancreatic diseases [210].

Nerve invasion

Neural invasion is a distinct route for the spread of pancreatic carcinoma. However, the clinicopathologic significance of neural invasion, with particular reference to intrapancreatic nerve invasion, remains to be elucidated. One hundred fifty-three patients who underwent pancreaticoduodenectomy for invasive ductal carcinoma of the pancreas between 2004 and 2008 were retrospectively examined. The clinical and histopathologic factors, including intrapancreatic nerve invasion, were analyzed in these patients. The relationships between the degree of intrapancreatic nerve invasion and disease-free survival, as well as various histopathologic factors, were investigated. There were significant differences in the degree of intrapancreatic nerve invasion with regard to disease-free survival. A lack of lymph node metastases, lower incidence of intrapancreatic nerve invasion, and negative surgical margin significantly increased the disease-free survival. The tumor stage was not associated with intrapancreatic nerve invasion. However, a larger tumor size, a higher incidence of lymphatic invasion, and the presence of extrapancreatic nerve plexus invasion were identified as independent factors associated with a higher incidence of intrapancreatic nerve invasion. It was concluded that intrapancreatic nerve invasion may be useful as a predictor for recurrence after pancreaticoduodenectomy in patients with invasive ductal carcinoma of the pancreas [211].

Socio-economic factors

There are several population-based data sets that have been studied to identify practice patterns and outcomes in pancreatic cancer. The strength of these studies lies in their sample size, which allows sufficient statistical power to examine questions that cannot be addressed in small randomized trials. Recent studies have suggested barriers to appropriate treatment of pancreatic cancer including: age, race, socioeconomic status, education, geographic location, and insurance status. However, there is limited information on the survival outcome of patients with potentially resectable, localized pancreatic cancer treated with nonsurgical therapy or who do not receive any therapy. It was identified 3204 patients in the California Cancer Registry with complete tumor and staging information and a diagnosis of localized adenocarcinoma of the pancreas in the state of California from 1994 to 2002. Among these 3204 patients with localized pancreatic cancer, 892 (28 %) underwent surgical resection with curative intent, whereas 2312 (62 %) did not; among these 2312 patients with localized pancreatic cancer who did not undergo surgical therapy, 1038 (32 % of the entire cohort) received chemotherapy and/or radiotherapy; 1274 patients (40 % of the entire cohort) received no tumor-directed therapy. Patients who underwent surgery had a significantly longer median overall survival than those who did not (18 vs 7 months). Two-year survival was 34 percent in the resected group versus 6 percent in the nonresected group. The median survival of patients undergoing chemoradiotherapy was 10 months compared with 5 months for no treatment, however. Patients who underwent multimodality treatment (surgery plus adjuvant therapy) had the longest median survival (23 vs 15 months for surgery alone). Younger patient age was associated with a higher probability of undergoing surgical therapy for localized pancreatic cancer; patients older than 75 years had an odds ratio of 0.21 of

undergoing surgical therapy compared with those younger than 60 years. The highest socioeconomic quintile had a 40 percent greater likelihood of undergoing surgical therapy compared with the lowest quintile. Interestingly, patients from rural areas and small towns (2500-10,000 residents) were more likely than urban residents to undergo surgical therapy (41 % vs 27 %). Black race was associated with the lowest rate of surgical therapy (23 % vs 28 % for all other groups). Unlike other reported series, there was no change in the rate of surgical therapy over the period of the study (1994-2002) [212].

Epidemiology and risk factors

Risk factors for this malignant disease include smoking, family history of chronic pancreatitis, advancing age, male gender, diabetes mellitus, obesity, non-O blood group,^{3,4} occupational exposures (e.g. to chlorinated hydrocarbon solvents and nickel), African-American ethnic origin, a high-fat diet, diets high in meat and low in vegetables and folate, and possibly *Helicobacter pylori* infection and periodontal disease. Coffee intake is not regarded as a risk factor for disease. Although the cause of pancreatic cancer is complex and multifactorial, cigarette smoking and family history are dominant. About 20 percent of pancreatic tumours are caused by cigarette smoking, and cancers from smokers harbour more genetic mutations than those from non-smokers. A family history of pancreatic cancer is an important risk factor for disease; about 7-10 percent of affected individuals have a family history [213].

Several risk factors have been reported regarding the development of pancreatic cancer. These risk factors include family history, accompanying diseases, and lifestyle/personal habits. Family history includes that of pancreatic cancer and hereditary pancreatic cancer syndrome. Accompanying diseases that increase the risk include diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatic cancer syndrome and intraductal papillary mucinous neoplasms. Lifestyle-associated factors include smoking and diet. Detailed examination of patients with such risk factors is warranted, but the cost-benefit effect should be considered. Thus, patients with more than one risk factor should be carefully followed up, and periodic examination of such patients is necessary to ensure the detection of smaller and less-advanced pancreatic cancer lesions and thus to improve the clinical outcome of patients with pancreatic cancer [214].

Reproductive and hormonal factors

To investigate the role of menstrual, reproductive, and hormonal factors, as well as benign female conditions, on pancreatic cancer risk it was analyzed the combined data from two Italian case-control studies including 285 female case patients of pancreatic cancer and 713 female controls. All subjects were interviewed by trained interviewers during their hospital stay using similar structured questionnaires. Odds ratios and their corresponding 95 percent confidence intervals were estimated using multiple logistic regression models adjusted for selected covariates. Compared to nulliparae, the OR was 0.76 (95 % confidence interval 0.51 to 1.12) for parous women and 0.46 (95 % confidence interval 0.26 to 0.85) for women with 4 or more births, in the absence, however, of a significant trend with increasing number of births. Pancreatic cancer risk was also nonsignificantly reduced among women with age at first birth lower than 25 years (OR, 0.65; 95 % confidence interval 0.42 to 1.01). Other factors, including age at menarche and menopause, menopausal status, type of menopause, history of spontaneous and induced abortions, use of oral contraceptives and hormone replacement therapy, and history of most female benign conditions were not related to pancreatic cancer risk. The study provides little support for the hypothesis that menstrual, reproductive, or hormonal factors are related to the development of pancreatic cancer [215].

Helicobacter pylori

Helicobacter pylori infection is associated with gastric cancer. A total of 97 percent of the infected subjects have elevated levels of *H. pylori* antibodies. The antibody titers have been shown to decline rapidly (40-60 % within 4-12 months) only after successful eradication therapy. It was allocated 26,700 consecutive patients tested during 1986-1998 for *H. pylori* antibodies to 3 subcohorts: seropositive patients with rapidly falling antibody titers (Hp+CURED, n=3,650), seropositive patients where no serological information indicating cure was obtained (Hp+NoInfo, n=11,638) and seronegative patients (Hp-, n=11,422). In the subcohorts, the standardised incidence ratios (SIRs) with 95 % confidence intervals (CI) were defined for subsequent cancers of stomach, pancreas, colon, rectum, breast and prostate separately and for all cancers except stomach combined. The mean follow-up time was 10.1 years and the number of gastric cancers was 72. For the Hp+CURED, the SIR for gastric cancers for the first 5 follow-up years was 1.62 but decreased from the sixth follow-up year thereon to 0.14 (95 % confidence interval 0.00 to 0.75). Likewise, the risk ratio, defined in a Poisson regression analysis using the Hp+NoInfo group as the reference, decreased from 1.60 to 0.13. The SIR for Hp- was not significantly higher than that for Hp+NoInfo for any of the cancers analysed. To conclude, cured *H. pylori* infection led to a significantly decreased incidence of gastric cancers from the sixth follow-up year. Advanced atrophic gastritis would be a plausible contributor to the elevated SIR in elderly Hp- patients [216].

Diabetes

Although half of all patients with pancreatic cancer are diabetic at the time of diagnosis, it remains unclear whether the diabetes associated with pancreatic cancer is a cause or an effect of the malignancy. Epidemiologic studies were reviewed, the geographic prevalence of diabetes and the incidence of pancreatic cancer were examined, and clinical and laboratory studies were reviewed. Long-standing diabetes increases the risk of pancreatic cancer by 40 percent to 100 percent, and recent-onset diabetes is associated with a 4- to 7-fold increase in risk, such that 1 to 2 percent of patients with recent-onset diabetes will develop pancreatic cancer within 3 years. Treatment of diabetes or morbid obesity decreases the risk of pancreatic cancer, and metformin therapy decreases the risk due to both its antidiabetic and antineoplastic effects. Recent-onset diabetes associated with pancreatic cancer likely represents secondary or type 3 diabetes. The discrimination of type 3 diabetes from the more prevalent type 2 diabetes may identify the high-risk subgroup of diabetic patients in whom potentially curable pancreatic cancer may be found. It was concluded that type 2 and type 1 diabetes mellitus increase the risk of pancreatic cancer with a latency period of more than 5 years. Type 3 diabetes mellitus is an effect, and therefore a harbinger, of pancreatic cancer in at least 30 percent of patients [217].

Prior studies of cancer risk among diabetic men have reported inconsistent findings. The aim of this study was to assess the risk of cancer among a large cohort (n=4,501,578) of black and white U.S. veterans admitted to Veterans Affairs hospitals. The cancer risk among men with diabetes (n=594,815) was compared to the risk among men without diabetes (n=3,906,763). Poisson regression was used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs). Overall, men with diabetes had a significantly lower risk of cancer (RR = 0.93, 95 % confidence interval = 0.9 to 0.94). Men with diabetes, however, had increased risks of cancers of the liver (pancreas; relative risk 1.50, 95 % confidence interval 1.42 to 1.59), biliary tract, colon, rectum, and kidney, as well as leukemia, and melanoma. In contrast, men with diabetes had decreased risks of cancers of the prostate, buccal cavity, lung, esophagus, and larynx. These findings indicate that black and white men with diabetes are at significantly lower risk of total cancer and of two of the most common cancers among U.S. males; lung and prostate cancers. These decreased risks were offset, however, by increased risks of cancer at several sites. Hyperinsulinemia may explain the increased risks of the digestive cancers, while lower testosterone levels, in the case of prostate cancer, and

higher BMI, in the case of lung cancer, may explain the decreased risks of those tumors [218].

Epidemiological studies have demonstrated that diabetes is a risk factor for multiple forms of malignancy including pancreatic cancer. Inoue et al documented significantly increased relative risks of developing liver, pancreas, and kidney cancer associated with a history of diabetes among 97,771 Japanese adults surveyed and then followed for 10 years. Data from the CLUE II cohort of 32,894 individuals in Maryland showed that the relative risk of diabetics developing any cancer was 1.3 times that of non-diabetic individuals. Diabetic patients in this population had a 2.5-fold increased risk of developing pancreatic cancer compared to non-diabetics. The degree of glycemic control appears to proportionally influence the risk of developing several cancer types, suggesting that diabetes may contribute to the formation of certain cancers through the effects of chronic hyperglycemia and/or hyperinsulinemia. Batty et al in England found evidence for a graded dose-response relationship between fasting glucose and the development of pancreatic or liver cancer resulting in mortality, and Jee et al similarly found a positive linear relationship between fasting glucose and the risk of developing pancreatic cancer across all categories of obesity in a cohort analysis of 1,298,385 Korean patients. In 2005, Stolzenberg-Solomon et al examined the risk of pancreatic cancer associated with basal glucose levels, basal insulin levels, and the degree of insulin resistance in 29,133 male Finnish smokers followed for over 10 years. Diabetic subjects were found to have a hazard ratio of 2.13 overall, with increased risk seen for increases in all three basal measurements. However, the increased risks of hyperglycemia, hyperinsulinemia, and insulin resistance did not reach statistical significance until more than 10 years had elapsed, suggesting that long-standing impairments were associated with the development of pancreatic neoplasia [030].

The relationships between diabetes and pancreatic cancer were recently corroborated in a study of pancreatic ductal pathology by Butler et al who examined the expression of the neoplastic markers cytokeratin and Ki-67 in pancreatic ductal epithelia from 45 human autopsy and 9 surgical pathology specimens. In autopsy specimens obtained from obese non-diabetic individuals, pancreatic duct replication was seen to be increased 10-fold compared to lean non-diabetics, whereas in lean diabetics, duct epithelia replication was increased 4-fold compared to lean non-diabetic subjects. These results indicate the independent effects of obesity and longstanding diabetes on the replication rate in pancreatic ductal cells, and presumably therefore the likelihood of the development of pancreatic exocrine neoplasia. Markers of pancreatic ductal replication were increased synergistically in obese diabetic subjects. When surgical specimens of chronic pancreatitis or non-tumor tissue adjacent to pancreatic cancer were examined, even higher rates of the expression of replication markers were seen, which supports the roles of chronic pancreatitis and diabetes as contributory to oncogenesis [030].

Recent studies provide insight into how insulin-activated enhancement of cell proliferation is increased in pancreatic and other malignancies, and the role of insulin/insulin-like growth factor-1 (IGF-1) receptor regulation of neoplastic behavior. The insulin-like growth factor receptor (IGFIR), a tyrosine kinase receptor for IGF-1 and IGF-2, has been well documented in cell culture, animal studies, and humans to play a role in malignant transformation, progression, protection from apoptosis, and metastasis. In addition, the hormone insulin and its tyrosine kinase receptor (IR) have been documented both in vitro and in vivo to play a key role in cancer biology. Interestingly, one of the two IR isoforms (IR-A) is especially overexpressed in cancers including pancreatic adenocarcinoma. IR-A is the IR fetal isoform and has the peculiar characteristic to bind not only insulin but also IGF-2. In addition, the IR expressed in malignant tissue has the capacity to form a hybrid receptor with the IGF-IR. By binding to hybrid receptors, insulin may stimulate specific IGF-IR signaling pathways which mediate cell proliferation, inhibition of apoptosis, and growth. Therefore, hyperinsulinemia,

associated with insulin resistance and obesity, should be treated by changes in lifestyle and/or pharmacological approaches to avoid an increased risk for cancer [030].

New-onset diabetes mellitus (DM) may herald pancreatic cancer (PaC). It was determined whether changes in body weight distinguished PaC-associated DM (PaCDM) from type 2 DM. Among Olmsted County residents, it was identified 29 PaCDM and 43 type 2 DM subjects who had serial fasting blood glucose measurements, new-onset DM, and no cancer-specific symptoms at DM onset. It was compared body weight (kg) and fasting blood glucose (mg/dL) at DM onset, 1 to 2 years before and at index date in the 2 groups. Fasting blood glucose values were similar before and at the onset of DM. Before onset of DM, PaCDM and type 2 DM subjects had similar body weight. However, at onset of DM, 59 percent of PaCDM subjects lost weight versus 30 percent of type 2 DM subjects, which was a significant difference. At onset of DM, 56 percent of type 2 DM subjects gained weight versus 31 percent of PaCDM subjects. By index date, PaCDM subjects lost more weight than type 2 DM subjects did. Thus, although new-onset primary type 2 DM is typically associated with weight gain, weight loss frequently precedes onset of PaCDM. The paradoxical development of diabetes in the face of ongoing weight loss may be an important clue to understanding the pathogenesis of PaCDM [219].

Metformin and pancreatic cancer

In 2005, Evans et al evaluated metformin use in diabetics who were admitted to hospital with a diagnosis of cancer between 1993 and 2001 in Tayside, Scotland, and compared this cohort with diabetic controls who were not admitted for cancer. They found that any exposure to metformin was associated with a significant reduction in cancer risk (RR 0.77). The data also suggested a dose-response relationship between metformin dosage, or number of metformin prescriptions, and a reduction in cancer risk, presumably due to the successful reduction of chronic hyperglycemia. When the outcome of 4,804 metformin users was compared to 4,085 non-users, a reduced risk (RR 0.63) for cancer mortality was found among diabetic patients treated with metformin, whereas a (non-significantly) increased risk of cancer mortality was seen among insulin and sulfonylurea users. These clinical studies corroborated the findings of Schneider et al who found a therapeutic effect of metformin in a hamster model of pancreatic carcinoma. In these animals, metformin treatment significantly decreased islet cell hyperplasia and pancreatic ductal proliferation and completely prevented the development of pancreatic adenocarcinoma. Metformin is a biguanide derivative which has been used for the treatment of T2DM for 50 years. Its primary action is to inhibit hepatic glucose production but it also increases the sensitivity of peripheral tissues to insulin. Metformin activates the liver kinase B1-adenyl monophosphate (LKB1-AMP) protein-activated kinase (AMPK) pathway, which serves not only to suppress hepatic glucose production and reduce the need for insulin-mediated glucose transport, but also to inhibit the signaling mechanisms which regulate cellular proliferation. These pathways are critical regulators of cell replication, and have been found to be inhibited by metformin in pancreatic cancer cells. Maida et al report that metformin also acutely increases plasma levels of GLP-1 in mice. Moreover, they show that metformin enhances the expression of the genes encoding the receptors for both GLP-1 and GIP in mouse islets which increases the effects of GIP and GLP-1 on insulin secretion from beta-cells [030].

Sweetened beverages

Soft drinks usually contain sugar and caffeine that might influence pancreatic carcinogenesis. It was considered the association between carbonated drink consumption and pancreatic cancer risk in an Italian case-control study conducted in 1991-2008 on 326 pancreatic cancer cases and 652 matched controls. It was also combined the results from all the studies on soft drinks or sweetened beverages and pancreatic cancer published before June 2010, using a meta-analytic approach. In the case-control study, compared with non-drinkers, the multivariate odds ratio was 1.02 (95 % confidence interval 0.72 to 1.44) for carbonated drink

consumers and 0.89 (95 % confidence interval 0.53 to 1.50) for regular consumers (at least one drink/day). Besides our study, from the literature search, it was identified 4 other case-control (1,919 cases) and 6 cohort studies (2,367 cases). The pooled relative risks (RR) for soft drink consumers vs. non-consumers were 0.97 (95 % confidence interval 0.81 to 1.16) for case-control, 1.05 (95 % confidence interval 0.94 to 1.17) for cohort, and 1.02 (95 % confidence interval 0.93 to 1.12) for all studies. The pooled RRs for heavy drinkers were 1.08 (95 % confidence interval 0.73 to 1.60) for case-control, 1.21 (95 % confidence interval 0.90 to 1.63) for cohort, and 1.16 (95 % confidence interval 0.93 to 1.45) for all studies. In conclusion, soft drink consumption is not materially related to pancreatic cancer risk [220].

Smoking

Cigarette smoking has been recognized as an important risk factor for pancreas cancer, but the magnitude of the association may vary among geographical areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and pancreas cancer in the Japanese population. Original data were obtained from MEDLINE searched using PubMed or from searches of the Ichushi database, complemented with manual searches. Evaluation of associations was based on the strength of evidence (“convincing”, “probable”, “possible” or “insufficient”) and the magnitude of association (“strong”, “moderate”, “weak” or “no association”), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer. It was identified four cohort studies and three case-control studies. All cohort studies consistently showed positive associations between pancreas cancer and cigarette smoking, although statistical significance in each study is variable. Most of the cohort studies consistently showed that cigarette smoking had a dose-response relationship with pancreas cancer. One case-control study showed a strong positive association, but the rest did not show any association. Meta-analysis of seven studies indicated that a summary estimate for ever smoking relative to never smoking was 1.68 (95 % confidence interval 1.38 to 2.05). It was concluded that there is convincing evidence that cigarette smoking moderately increases the risk of pancreas cancer in the Japanese population [221].

To examine the association of smoking and lifestyle factors with pancreatic cancer death in the prospective design. Mortality from pancreatic cancer in regard to smoking, body mass index, physical activity, and alcohol, coffee and green tea intake, was studied in a prospective cohort of 30,826 inhabitants in Takayama, Japan. In 1992, each subject completed a self-administered questionnaire on demographic information, smoking, drinking habits, diet, exercise and medical histories. The response rate was 85 percent. From 1992 to 1999, 33 men and 19 women died due to pancreatic cancer. Women who were defined as current smokers at baseline had significant and increased risk of pancreatic cancer death after adjustment for age, body mass index and history of diabetes mellitus. There were significant positive associations of pancreatic cancer death with the years of smoking and the number of cigarettes consumed daily in women in a dose-dependent manner. Current smokers indicated a non-significant risk increase in men. Body mass index, physical activity, and alcohol, coffee and green tea intake were not significantly associated with pancreatic cancer death. These data suggested that smoking increases the risk of death from pancreatic cancer in Japanese women [222].

Nicotine

Osteopontin (OPN) is a secreted phospho-protein that confers on cancer cells a migratory phenotype. It has recently shown that nicotine, a risk factor in pancreatic ductal adenocarcinoma (PDA), induces an alpha7-nicotine acetylcholine receptor (alpha7-nAChR)-mediated increase of OPN in PDA cells. In this study, it was tested nicotine's effect on the expression of OPN splice variants (OPNa, b, c) in PDA cells. It was also analyzed the correlation between patients' smoking history with OPN and alpha7-nAChR levels. RT-PCR

and UV-light-illumination of ethidium-bromide staining were used to examine the mRNA expression in tissue and PDA cells treated with or without nicotine (3-300 nM). Localization of total OPN, OPNc and alpha7-nAChR was analyzed by immunohistochemistry, and their mRNA tissue expression levels were correlated with the patients' smoking history. PDA cells expressed varying levels of OPNa, OPNb, and alpha7-nAChR. Nicotine treatment selectively induced denovo expression of OPNc and increased alpha7-nAChR expression levels. In PDA tissue, OPNc was found in 87 percent of lesions, of which 73 percent were smokers. OPNc and total OPN levels were correlated in the tissue from patients with invasive PDA. Nicotine receptor was expressed in the invasive and premalignant lesions without clear correlation with smoking history. It was shown here for the first time that alpha7-nAChR is expressed in PDA cells and tissues and is regulated by nicotine in PDA cells. This, together with our previous findings that alpha7-nAChR mediates the metastatic effects of nicotine in PDA, suggest that combined targeting of alpha7-nAChR and OPNc could be a valid novel therapeutic strategy for invasive PDA, especially in the smoking population [223].

Alcohol

The Cancer Council Australia (CCA) Alcohol Working Group has prepared a position statement on alcohol use and cancer. The statement has been reviewed by external experts and endorsed by the CCA Board. Alcohol use is a cause of cancer. Any level of alcohol consumption increases the risk of developing an alcohol-related cancer; the level of risk increases in line with the level of consumption. It is estimated that 5070 cases of cancer (or 5 % of all cancers) are attributable to long-term chronic use of alcohol each year in Australia. Together, smoking and alcohol have a synergistic effect on cancer risk, meaning the combined effects of use are significantly greater than the sum of individual risks. Alcohol use may contribute to weight (fat) gain, and greater body fatness is a convincing cause of cancers of the oesophagus, pancreas, bowel, endometrium, kidney and breast (in postmenopausal women). The existing evidence does not justify the promotion of alcohol use to prevent coronary heart disease, as the previously reported role of alcohol in reducing heart disease risk in light-to-moderate drinkers appears to have been overestimated. CCA recommends that to reduce their risk of cancer, people limit their consumption of alcohol, or better still avoid alcohol altogether. For individuals who choose to drink alcohol, CCA recommends that they drink only within the National Health and Medical Research Council guidelines for alcohol consumption [224].

Micronutrients

Several studies have shown an inverse relation between vegetable and fruit intake and pancreatic cancer, but no specific beneficial component of such foods has been consistently identified. It was considered the role of 15 selected vitamins and carotenoids and 6 minerals on pancreatic cancer risk in an Italian case-control study. The subjects were 326 patients with incident pancreatic cancer and 652 controls, admitted to the same hospitals as cases for acute conditions. Micronutrient computation was based on a validated and reproducible food-frequency questionnaire. It was estimated the odds ratios (OR) and confidence intervals (CI) using conditional logistic regression models, adjusted for various confounding factors and for energy intake, according to the residual model. Comparing the highest to the lowest quintile of intake, the OR were 0.60 (95 % confidence interval 0.36 to 0.98) for vitamin E, 0.44 (95 % confidence interval 0.27 to 0.73) for vitamin C, 0.56 (95 % confidence interval 0.34 to 0.93) for folate, and 0.57 (95 % confidence interval 0.35 to 0.92) for potassium. No significant inverse associations were observed for α -carotene (OR = 0.69, 95 % confidence interval 0.43 to 1.12), β -carotene (OR = 0.64, 95 % confidence interval 0.39 to 1.06), and β -cryptoxanthin (OR = 0.66, 95 % confidence interval 0.39 to 1.09). No relation was found for other micronutrients considered. The findings support a favorable role of vitamins E and C, selected carotenoids, and folate on pancreatic carcinogenesis [225].

Blood groups

The aim of one study was to determine the association between ABO blood group and the risk and progression of pancreatic ductal adenocarcinoma (PDAC) in the Han Chinese ethnic group. During the period of 2000-2009, 1,431 patients with PDAC and 1,449 age- and sex-matched controls were recruited in two university-affiliated hospitals. An unconditional multivariable logistic regression analysis was used to estimate adjusted odds ratios (ORs). The relationship between patient ABO blood group and clinicopathologic features was also analyzed. Compared with subjects having blood group O, a modestly higher risk was observed among cases with blood group A or AB with adjusted ORs (95 % confidence interval) of 1.368 (1.127 to 1.661) and 1.391 (1.053 to 1.838), respectively. The TNM stages of tumors in patients with non-O blood groups (A, B or AB) were more highly advanced than in patients with blood group O. Among patients who underwent a potentially curative operation, the median survival time of patients with blood group O was significantly longer than that of patients with non-O blood groups (16 months vs 11 months). The study shows evidence of an association between blood group type and risk for development and progression of PDAC. These findings merit further confirmation in a large population-based prospective study in patients of the Han Chinese ethnic group [226].

Several studies have investigated a possible association between the ABO blood group and the risk of pancreatic cancer (PC), but this association has not been fully evaluated in Asian populations. The present study aimed to assess the impact of genotype-derived ABO blood types, particularly ABO alleles, on the risk of PC in a Japanese population. It was conducted a case-control study using 185 PC and 1465 control patients. Using rs8176719 as a marker for the O allele, and rs8176746 and rs8176747 for the B allele, all participants' two ABO alleles were inferred. The impact of ABO blood type on PC risk was examined by multivariate analysis, with adjustment for potential confounders to estimate odds ratios and 95 percent confidence intervals. An increased risk of PC was observed with the addition of any non-O allele. Compared with subjects with the OO genotype, those with AO and BB genotypes had significantly increased OR of 1.67 and 3.28, respectively. Consistent with earlier reports showing a higher risk of PC for individuals with the non-O blood type, the previously reported protective allele (T) for rs505922 was found to be strongly correlated with the O allele. In conclusion, this case-control study showed a statistically significant association between ABO blood group and PC risk in a Japanese population [227].

Obesity

Epidemiologic studies of pancreatic cancer risk have reported null or nonsignificant positive associations for obesity, while associations for height have been null. Waist and hip circumference have been evaluated infrequently. A pooled analysis of 14 cohort studies on 846,340 individuals was conducted; 2,135 individuals were diagnosed with pancreatic cancer during follow-up. Study-specific relative risks (RRs) and 95 percent confidence intervals were calculated by Cox proportional hazards models, and then pooled using a random effects model. Compared to individuals with a body mass index (BMI) at baseline between 21 and 23, pancreatic cancer risk was 47 percent higher among obese individuals. A positive association was observed for BMI in early adulthood (pooled multivariate RR 1.30 comparing BMI to a BMI between 21 and 23. Compared to individuals who were not overweight in early adulthood (BMI < 25) and not obese at baseline (BMI < 30), pancreatic cancer risk was 54 percent higher for those who were overweight in early adulthood and obese at baseline. It was observed a 40 percent higher risk among individuals who had gained BMI \geq 10 between BMI at baseline and younger ages compared to individuals whose BMI remained stable. Results were either similar or slightly stronger among never smokers. A positive association was observed between waist to hip ratio (WHR) and pancreatic cancer risk (pooled RR 1.35 comparing the highest versus lowest quartile). BMI and WHR were positively associated with

pancreatic cancer risk. Maintaining normal body weight may offer a feasible approach to reducing morbidity and mortality from pancreatic cancer [228].

The relationship between two measures of excess body weight, body mass index (BMI) and body size score, and risk of pancreatic cancer was examined among 574 pancreatic cancer cases and 596 frequency-matched controls from the Czech Republic and Slovakia enrolled between 2004 and 2009. Analyses using multivariable logistic regression showed an increased risk of pancreatic cancer associated with elevated quartiles of BMI at ages 20 (fourth quartile: odds ratio, OR, 1.79) and 40 (fourth quartile: OR 1.57) compared to the lowest quartile. Consistent results were observed for body size score at ages 20 (high versus low: OR 1.66) and 40 (medium versus low: OR 1.36), but no association was found for BMI and body size score at 2 years before the interview. Stronger risk estimates for BMI were observed in males than females, particularly at age 20, but the analysis of body size yielded similar estimates by sex. When considering excess body weight at both ages 20 and 40 jointly, the highest risk estimates were observed among subjects with elevated levels at both time periods in the analysis of BMI (OR 1.86) and body size (OR 1.53). These findings, based on two different measures, provide strong support for an increased risk of pancreatic cancer associated with excess body weight, possibly strongest during early adulthood [229].

Increased body mass index (BMI) indicative of overweight (25-29.9 kg/m²) or obesity (≥30 kg/m²) is associated with numerous types of cancer. A 2010 pooled analysis from PanScan demonstrated that anthropometric factors impact the likelihood of developing pancreatic adenocarcinoma. Using a nested case-control design of 2170 cases and 2209 controls, researchers observed a positive association between prediagnosis BMI and risk of pancreatic cancer (adjusted OR for highest vs lowest BMI quartile, 1.33; 95 % confidence interval 1.12 to 1.58). Elevated BMI and increasing trends for pancreatic cancer were noted among both men and women. Higher waist-to-hip ratio was also significantly associated with pancreatic cancer risk among women (adjusted OR for highest vs lowest quartile in women, 1.87; 95 % confidence interval 1.31 to 2.69) but not among men. Hypotheses have been offered regarding the relationship between higher BMI and pancreatic cancer, including increases in insulin-like growth factors due to hyperglycemia, imbalances in adipokines, and the low-grade systemic inflammation that is fostered by states of obesity. Obesity itself predisposes to type 2 diabetes mellitus, a recognized risk factor for pancreatic cancer. Continuing prospective studies may provide additional proof for the association [203].

In connection with diabetes mellitus

Many risk factors have been associated with PC. Interestingly, large numbers of epidemiological studies suggest that obesity and diabetes, especially type-2 diabetes, are positively associated with increased risk of PC. Similarly, these chronic diseases (obesity, diabetes, and cancer) are also a major public health concern. In the U.S. population, 50 percent are overweight, 30 percent are medically obese, and 10 percent have diabetes mellitus (DM). Therefore, obesity and DM have been considered as potential risk factors for cancers; however, the focus of this article is restricted to PC. Although the mechanisms responsible for the development of these chronic diseases leading to the development of PC are not fully understood, the biological importance of the activation of insulin, insulin like growth factor-1 (IGF-1) and its receptor (IGF-1R) signaling pathways in insulin resistance mechanism and subsequent induction of compensatory hyperinsulinemia has been proposed. Therefore, targeting insulin/IGF-1 signaling with anti-diabetic drugs for lowering blood insulin levels and reversal of insulin resistance could be useful strategy for the prevention and/or treatment of PC. A large number of studies have demonstrated that the administration of anti-diabetic drugs such as metformin and thiazolidinediones (TZD) class of PPAR-gamma agonists decreases the risk of cancers, suggesting that these agents might be useful anti-tumor agents for the treatment of PC. In one review article, it was discussed the potential roles of metformin and TZD anti-diabetic drugs as anti-tumor agents in the context

of PC and will further discuss the complexities and the possible roles of microRNAs (miRNAs) in the pathogenesis of obesity, diabetes, and PC [230].

Metabolic syndrome

It was assessed the relation between metabolic syndrome (MetS), its components, and pancreatic cancer risk in an Italian case-control study and performed a meta-analysis of epidemiological studies published up to February 2011. The case-control study included 326 patients with incident pancreatic cancer and 652 controls admitted to the same hospitals for acute, non-neoplastic conditions. MetS was defined as having at least 3 conditions among diabetes, drug-treated hypertension, hyperlipidemia, and body mass index at least 25 kg/m² at age 30 years. It was computed multivariate odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs) from logistic regression models adjusted for tobacco smoking, education, and other sociodemographic variables. For the meta-analysis, we calculated summary relative risks (RRs) using random-effects models. The OR of pancreatic cancer in the case-control study was 2.36 for diabetes, 0.77 for hypertension, 1.38 for hypercholesterolemia, and 1.27 for being overweight at age 30 years. The risk was significantly increased for subjects with 3 or more MetS components (OR 2.13) compared with subjects with no component, the estimates being consistent among strata of gender, age, and alcohol consumption. The meta-analysis included 3 cohort studies and our case-control study, and found a summary RR of 1.55 for subjects with MetS. Metabolic syndrome is related to pancreatic cancer risk. Diabetes is the key component related to risk [231].

Physical activity

One review evaluated the current understanding of the benefits and risks of physical activity and exercise on the gastrointestinal system. A significant portion of endurance athletes are affected by gastrointestinal symptoms, but most symptoms are transient and do not have long-term consequences. Conversely, physical activity may have a protective effect on the gastrointestinal system. There is convincing evidence that physical activity reduces the risk of colon cancer. The evidence is less convincing for gastric and pancreatic cancers, gastroesophageal reflux disease, peptic ulcer disease, nonalcoholic fatty liver disease, cholelithiasis, diverticular disease, irritable bowel syndrome, and constipation. Physical activity may reduce the risk of gastrointestinal bleeding and inflammatory bowel disease, although this has not been proven unequivocally. This article provides a critical review of the evidence-based literature concerning exercise and physical activity effects on the gastrointestinal system and provides physicians with a better understanding of the evidence behind exercise prescriptions for patients with gastrointestinal disorders. Well-designed prospective randomized trials evaluating the risks and benefits of exercise and physical activity on gastrointestinal disorders are recommended for future research [232].

Cholecystectomy

Patients with pancreatic cancer who present with biliary symptoms may undergo cholecystectomy and thus delay cancer diagnosis. It was hypothesized that prior cholecystectomy leads to decreased overall survival in patients with pancreatic adenocarcinoma. Three hundred sixty-five patients with a diagnosis of resectable periampullary pancreatic adenocarcinoma were identified. Eighty-seven patients underwent prior cholecystectomy. Median age, body mass index (BMI), diabetes status, American Society of Anesthesiologists (ASA) class, stent placement, operative time, estimated blood loss (EBL), intraoperative transfusion, portal vein resection, LOS, adjuvant therapy, tumor size, differentiation, angiolymphatic invasion, perineural invasion, nodal metastasis, complication rate, and 30-day mortality were not statistically different between patients with previous cholecystectomy and those without. Median survival was 14 months for patients

with a history of cholecystectomy and 16 months for those without. Thus, previous cholecystectomy was not a predictor of survival on Cox regression analysis [233].

Dietary folate is essential for DNA methylation, synthesis, and repair, and inadequate intake may drive carcinogenesis. Two recent studies determined that higher folate intake may be related to decreased risk of pancreatic cancer. Oaks et al examined dietary folate and pancreatic cancer risk among the 51,988 male and 57,187 female participants in the Prostate, Lung, Colon, Ovary (PLCO) trial. Using Cox proportional hazards ratio, they found that the highest compared with the lowest quartile of food folate intake was associated with a significantly decreased pancreatic cancer risk among women (≥ 253 compared with ≤ 179 microg/d; HR 0.47; 95 % confidence interval 0.23 to 0.94) but not among men (≥ 230 compared with ≤ 158 microg/d; HR 1.20; 95 % confidence interval 0.70 to 2.04). Gong et al published a large case-control study involving residents of the San Francisco Bay area. Using a semiquantitative food questionnaire, they determined that dietary folate was significantly inversely associated with pancreatic cancer (fifth vs first quintile of intake: OR 0.67; 95 % confidence interval 0.48 to 0.93) [203].

Vitamin D

The aim of one study was to evaluate a complex association among intake of dietary vitamin D, calcium, and retinol, and pancreatic cancer risk. Pancreatic cancer cases ($n=532$) diagnosed in 1995-1999 were identified using rapid case ascertainment methods and were frequency matched to population-based controls ($n=1,701$) in the San Francisco Bay Area. Detailed dietary data were collected during in-person interviews using a validated semi-quantitative food-frequency questionnaire. Adjusted unconditional logistic regression was used to estimate odds ratios (ORs) and confidence intervals. In men, increased pancreatic cancer risk was associated with currently recommended dietary vitamin D intake levels (highest (≥ 450 IU/day) vs lowest (<150 IU/day) intake, OR = 2.6) and total vitamin D intake from diet and supplements (for <800 IU/day). ORs for dietary vitamin D intake remained increased after adjustment for intake of retinol and calcium, although confidence intervals included unity. Stratified analyses showed that ORs were higher among men with lower intake of retinol and lower physical activity but there was no evidence of statistical interaction. No associations with vitamin D intake were observed among women, although ORs typically were elevated. ORs increased with increased dietary calcium intake among men and not women. The results among men showing an increased risk of pancreatic cancer associated with dietary intake of vitamin D and of calcium require confirmation in further studies. Continued investigation is needed to clarify the complex role of vitamin D and calcium in pancreatic cancer risk and to determine their optimal intake level and preventive effects for pancreatic cancer [234].

Vitamin D has been touted as a “wonder nutrient,” capable of fighting osteoporosis, heart disease, kidney disease, memory loss, and diabetes. Laboratory studies demonstrate that vitamin D may function in an antineoplastic manner by inducing cellular differentiation, initiating apoptosis, and inhibiting proliferation and angiogenesis. Additional epidemiologic studies show that vitamin D is associated with decreased risks of colon, breast, ovarian, and prostate cancers, although the evidence of a protective effect on pancreatic carcinogenesis has been inconsistent. In a 2010 study published in the British Journal of Cancer, Bao et al evaluated the predicted 25(OH)D levels in 118,597 participants in the combined Nurses’ Health Study and Health Professionals Follow-up Study from 1986 to 2006. Their predicted value was based on both dietary intake and sunlight exposure and was derived by using linear regression with the dependent variable as the serum sample 25(OH)D level of 1095 men who were free of cancer at the time of the blood draw, and the independent variables of race, geographic region, vitamin D intake, BMI, and physical activity. During 20 years of follow-up, 575 incident pancreatic cancers occurred; compared with the lowest quintile,

participants in the highest quintile of 25(OH)D had an adjusted risk ratio of 0.65 (95 % confidence interval 0.50 to 0.86) [203].

Coffee

To evaluate the association between coffee, decaffeinated coffee, and tea consumption and pancreatic cancer risk in a pooled analysis of two Italian case-control studies, between 1983 and 2008, it was conducted two case-control studies in Northern Italy, including a total of 688 pancreatic cancer cases and 2204 hospital controls with acute, non-neoplastic diseases. We computed multivariate odds ratios (ORs) and 95 percent confidence intervals (CIs) for coffee drinking (mostly espresso and mocha), adjusting for age, sex, center, year of interview, education, body mass index, tobacco smoking, alcohol drinking, and diabetes. Compared with coffee nondrinkers, the multivariate OR for coffee drinkers was 1.34 (95 % confidence interval 1.01 to 1.77). However, there was no trend in risk with respect to dose and duration. The OR for an increment of one cup per day was 1.05 (95 % confidence interval 0.98 to 1.11). There was no heterogeneity in strata of age, gender, and other covariates, including tobacco smoking. No association emerged for decaffeinated coffee (for drinkers the OR was 0.87, 95 % confidence interval 0.60 to 1.26, compared with decaffeinated coffee nondrinkers) or tea (for tea drinkers the OR was 0.92, 95 % confidence interval 0.75 to 1.14). The lack of relationship with dose and duration weighs against a causal association between coffee and pancreatic cancer, which is in agreement with most evidence on the issue [235].

Nitrite

Nitrate and nitrite are precursors of N-nitroso compounds, which induce tumors of the pancreas in animals. The authors evaluated the relation of dietary nitrate and nitrite to pancreatic cancer risk in the NIH-AARP Diet and Health Study. Nitrate and nitrite intakes were assessed at baseline using a 124-item food frequency questionnaire. During approximately 10 years of follow-up between 1995 and 2006, 1,728 incident pancreatic cancer cases were identified. There was no association between total nitrate or nitrite intake and pancreatic cancer in men or women. However, men in the highest quintile of summed nitrate/nitrite intake from processed meat had a nonsignificantly elevated risk of pancreatic cancer (hazard ratio = 1.18, 95 % confidence interval 0.95 to 1.47). The authors observed a stronger increase in risk among men for nitrate/nitrite intake from processed meat at ages 12-13 years (highest quintile vs lowest: hazard ratio 1.32, 95 % confidence interval 0.99 to 1.76), though the relation did not achieve statistical significance. The authors found no associations between adult or adolescent nitrate or nitrite intake from processed meats and pancreatic cancer among women. These results provide modest evidence that processed meat sources of dietary nitrate and nitrite may be associated with pancreatic cancer among men and provide no support for the hypothesis in women [236].

Folate

Folate intake has shown an inverse association with pancreatic cancer; nevertheless, results from plasma measurements were inconsistent. The aim of this study is to examine the association between plasma total homocysteine, methionine, folate, cobalamin, pyridoxal 5'-phosphate, riboflavin, flavin mononucleotide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). It was conducted a nested case-control study in the EPIC cohort, which has an average of 10 years of follow-up (1992-2006), using 463 incident pancreatic cancer cases. Controls were matched to each case by center, gender, age (± 1 year), date (± 1 year) and time (± 3 h) at blood collection and fasting status. Conditional logistic regression was used to calculate the odds ratios (OR), adjusting for education, smoking status, plasma cotinine concentration, alcohol drinking, body mass index and diabetes status. We observed a U-shaped association between plasma folate and pancreatic cancer risk. The ORs for plasma folate ≤ 5 , 5-10, 10-15 (reference), 15-20, and $>$

20 nmol/L were 1.58 (95 % confidence interval 0.72 to 3.46), 1.39 (95 % confidence interval 0.93 to 2.08), 1.0 (reference), 0.79 (95 % confidence interval 0.52 to 1.21), and 1.34 (95 % confidence interval 0.89 to 2.02), respectively. Methionine was associated with an increased risk in men (per quintile increment: OR=1.17, 95 % confidence interval 1.00-1.38) but not in women. The results suggest a U-shaped association between plasma folate and pancreatic cancer risk in both men and women. The positive association that we observed between methionine and pancreatic cancer may be sex dependent and may differ by time of follow-up. However, the mechanisms behind the observed associations warrant further investigation [237].

Poultry workers

To test the hypothesis that exposure to poultry oncogenic viruses that widely occurs occupationally in poultry workers and in the general population, may be associated with increased risks of deaths from liver and pancreatic cancers, and to identify new risk factors a pilot case-cohort study of both cancers within a combined cohort of 30,411 highly exposed poultry workers and 16,408 control subjects was conducted, and risk assessed by logistic regression odds ratios (OR) and proportional hazards risk ratios. New occupational findings were recorded respectively for pancreatic cancers, for slaughtering of poultry (OR 8.9, 95 % confidence interval 2.7 to 29) catching of live chickens (OR 3.6); killing other types of animals for food (OR 4.8) and ever worked on a pig raising farm (OR 3.0) for pancreatic cancer only. New non-occupational findings for liver cancer were for receiving immunization with yellow fever vaccine (OR 8.7); and vaccination with typhoid vaccine (OR 6.3). This study provides preliminary evidence that exposure to poultry oncogenic viruses may possibly be associated with the occurrence of pancreatic cancers. Case-control studies nested within occupational cohorts of highly exposed subjects of sufficient statistical power may provide an efficient and valid method of investigating/confirming these findings [238].

Theoretical pancreatic cancer biology

A new theory about tumor growth makes oncology look a little like cosmology. Just as the universe accelerates as it expands, tumors become malignant at an accelerating speed, according to a team of scientists who have been probing the mathematics of tumor growth. Bert Vogelstein, M.D., a Howard Hughes Medical Institute investigator, led the team of researchers from six institutions around the world who mapped tumor growth rates. In a model best described as a sequential driver mutation theory, they suggest mutations that drive tumor growth – called driver mutations – multiply sequentially over time, each one slightly increasing the tumor growth rate through a process that depends on the average of three factors: driver mutation rate, the 0.4% average selective growth advantage, and cell division time. Other models describe tumor dynamics as an exponential function or according to a Gompertz curve that shows how tumor growth gradually rises and levels off over time. But this theory is unique because it shows, for the first time, that a cancer cell with only one driver mutation will grow to only a certain size and then stop until another mutation happens. With a combination of experimental data and computer simulations, the group applied their theory to hypothetical patients with glioblastoma multiforme, pancreatic adenocarcinoma, and familial adenomatous polyposis (FAP), which can become malignant. In computational tests of both the brain and pancreatic cancers, a second driver mutation appeared 8.3 years after the first. But the mutation rate accelerated, with only 4.5 more years passing until the third driver mutation emerged. The researchers first demonstrated the ideas in six hypothetical patients with either glioma or pancreatic adenocarcinoma, finding enormous variation in the times required for disease progression. They used data from the Catalog of Somatic Mutations in Cancer (COSMIC) and a software program called CHASM, short for Cancer-specific High-throughput Annotation of Somatic Mutations that sorts and highlights

DNA changes most likely to promote cancer. CHASM examined 713 mutations sequenced from 14 glioma patients and 562 mutations in nine pancreatic adenocarcinoma patients. Using this information, the researchers estimated that roughly 100 tumor suppressor genes, 100 oncogenes, and 21,000 positions on the human genome can become driver mutations. Experimental evidence added the last variable: cell division time. It was shown that tumor cells in glioma divide about once every 3 days. The simulated decades of branching mutations returned the frustratingly heterogeneous scenarios oncologists observe in the clinic. In glioblastoma patient 1, a second driver mutation had not occurred within 20 years after tumor initiation, and the tumor remained microgram size. In glioblastoma patient 6, a second driver mutation occurred after only 2 years. At 20 years, the tumor would weigh in the kilograms. Patients 2–5 had progression rates between these two extremes. The team found similar results for the six pancreatic adenocarcinoma patients, confirming that the model helps provide an understanding of the heterogeneity in tumor sizes and development times observed by epidemiologists and clinicians. Selected driver mutations, tumor growth rates, and the estimated 0.4 percent selective growth advantage were plugged into the computer simulation model, a statistically driven mathematical program called the Galton–Watson process that described cancer growth in the hypothetical patients. Malignant progression in FAP follows a similar scenario. For years, a benign tumor may grow slowly but when it starts gathering new mutations, the growth process speeds up and leads to a malignant cancer fast. The idea is that cancerous mutations progress with the disease, thereby creating cumulative damage – rather than simply being a one-time force that pushes a boulder down a hill. The sequential driver mutation theory may also help efforts to “personalize” cancer genomics. One could foresee the capability to estimate how many driver mutations fuel specific types of cancer, and how long a specific type of cancer was present in someone. However, the advantage is not large enough to sustain tumor growth, which calls into question the long-held belief that tumors result from one or two mutations [239].

Transcriptional cancer biology

Every cancer reflects the highly heterogeneous make-up of the patient's genes, the stochastic mutational processes occurring within the tumour; the balance between these processes ultimately determining each tumour's unique profile. These inter-individual differences are evident in the variability of patient outcome. Under intensive investigation for the past decade, a wealth of information is now available on transcriptional regulation differences in tumourigenesis across multiple histological cancer types, cultured cells and xenograft models. Although critically needed to maximise cancer research, the interconnections between the molecular events that govern this transcriptional space in cancer are still largely unknown since most studies focus on molecular profiling a single sample type or condition. The same is true for non-malignant diseases where the amount of transcriptomic data obtained by molecular profiling a wide range of tissues and cells affected by the disease has grown exponentially. Despite the increasing wealth of available data, the structure of cancer transcriptional space remains largely unknown. Analysis of this space would provide novel insights into the complexity of cancer, assess relative implications in complex biological processes and responses, evaluate the effectiveness of cancer models and help uncover vital facets of cancer biology not apparent from current small-scale studies. There are two general approaches to comparative profiling analysis. The first method requires normalising and re-analysing the original data from each individual study. A limited number of meta-analyses tend to rely on this rigorous and reliable method because of problems associated with cross-platform analyses and most importantly the availability of both raw data and clinical information. The second approach is based on the assumption that essential genes will be consistently altered and relies on the identification of intersections between studies. While independent from the availability of raw data, this type of meta-analysis depends heavily on the pre-processing and analysis methods, the significance threshold and the annotation builds used in the original publication, not all of which are

always accurate and reproducible. A recent study has used the first method to produce a global map of human gene expression derived from the extensive analysis of 14 500 human genes across 5372 samples representing the structure of the expression space of 369 different cell and tissue types, disease states and cell lines. The authors showed that the major patterns are attributable to the tissue of origin independent of the disease state. It was conducted a comprehensive analysis of pancreatic cancer-expression space by integrating data from otherwise disparate studies. It was collected pancreatic-related expression data files from public repositories. These included 309 samples comprising of: four normal pancreas (commercial source); 55 normal-adjacent pancreas (pancreatic cancer patients); 96 pancreatic cancer [pancreatic cancer patients, representing 91 pancreatic ductal adenocarcinoma (PDAC) and five other pancreatic cancer types]; 65 pancreatic cancer cell lines (29 distinct cell lines); 24 saliva specimens (12 healthy subjects and 12 pancreatic cancer patients); 59 ectopic subcutaneous xenografts (pancreatic cancer patients) and six orthotopic xenografts (pancreatic cancer cell lines). It was found a clear separation of profiles based on experimental type, with patient tissue samples, cell lines and xenograft models forming distinct groups. PCA generated to view the underlying structure of the data showed two axes; microenvironment and malignancy, with patient tissue samples, xenograft models and cultured cell lines located in separate areas of the first empirical principal component and samples dispersed on the second empirical principal component based on their tumour content. It was found that the first two principal components explain about 42 percent of variability and have biological interpretations. Cross-validation showed that we do not appear to be overfitting the data by using two components. Closer inspection of profiles from histologically “normal-appearing” tissue adjacent to pancreatic cancer indicated the presence of three distinct subgroups (NAD1, NAD2 and NAD3). The first subgroup comprises of ND and the normal-adjacent samples whose profiles most closely resemble those of ND. Sample profiles in the second group (NAD2) are sufficiently different to NAD1 to form a distinct subgroup. The third subgroup (NAD3) reflects the expression profiles of samples most closely resembling those of PDAC. Additional analyses were implemented in an attempt to characterise this heterogeneity. The study encompasses the largest number of pancreatic-cancer profiles generated on a high-resolution expression array thereby ensuring that this is the most comprehensive analytical analysis of pancreatic cancer to date. By subjecting all the datasets from all the studies to the same rigorous quality control criteria and treating them jointly to a single, well-annotated, data processing pipeline, we have eliminated any differences in results attributable to analytical diversity. Furthermore, the increased statistical power and the capacity to generate comparisons not available from the disparate studies increase the ability to provide novel insights. This robust integrative analysis of multiple and diverse pancreatic cancer datasets has highlighted some important findings and issues. The main finding suggests that normal tissues, often used as a baseline against which cancer profiles are compared, may have already acquired a number of genetic alterations. This is of relevance not only in highlighting the possibility of “field change” in cancer, and the genes that characterise this, but importantly, that the ‘normal’ matched samples in many studies may not be an appropriate baseline for comparison with cancers. This may partially contribute to the lack of reproducibility between studies. We also show distinctions between profiles generated by studies based on cell lines and cell line-derived models to those using tumour samples. The ectopic subcutaneous xenograft models do not appear capable of accurately representing tumour behaviour, instead sharing greater similarities with pancreatic cancer cell lines. Initially conducted to provide an insight to the molecular events governing the transcriptional space of pancreatic cancer, this study serves to highlight concerns with the availability and quality of publicly accessible gene expression data. The main issue encountered was the lack of sufficient clinical and histopathological information available in the public domain, all of which act as a barrier to the accurate interpretation of cancer expression data. Similarly, a lack of detailed experimental and analytical documentation also hampers conclusive data evaluation and reproducibility. Attempts to overcome some of these limitations by obtaining access to additional clinical data were not met with success, precluding further investigation in the majority of cases. Heterogeneity of information

currently available to the pancreatic cancer community means that, while our findings are interesting, without additional documentation regarding these samples, accurate evaluations of the data are not possible [240].

Immunological aspects

To verify whether the dysregulation of CD4 T cells concurs in worsening the outcome of pancreatic cancer, we compared the effects of pancreatic cancer and other gastrointestinal cancer cell-conditioned media on the proliferation, migration, and differentiation of CD4 T cells and on expansion of CD4 memory (CD45RO), naive (CD45RA), activated (CD69), and regulatory (CD25) subsets. After culture of CD4 T cells in control, pancreatic (BxPC3, Capan1, MiaPaCa2), or gastrointestinal cancer (AGS, HepG2, HT29) cell-conditioned media, we evaluated proliferation, migration, interferon gamma (IFN-gamma) production, and CD45RA, CD45RO, CD69, and CD25 membrane expression in control and conditioned CD4 T cells. Only pancreatic cancer-conditioned media inhibited CD4 T-cell proliferation and migration under human stromal cell-derived factor- α chemotaxis and induced CD4 T-cell IFN-gamma production and the expansion of the CD69-positive subset with respect to the control, with no changes being found in the CD45RA, CD45RO, and CD25 subsets. Thus, the in vitro findings achieved in the present study demonstrate that pancreatic cancer cells inhibit CD4 T-cell proliferation and migration, induce IFN-gamma production, and favor a CD69 subset expansion, suggesting that CD4 T cells play an important role in pancreatic cancer immune evasion [241].

Common “themes” in epidemiology related to cancer risk beg a comprehensive mechanistic explanation. As people age, risk for cancer increases. Obesity and smoking increase the risk for many types of cancer. History of febrile childhood diseases lowers the risk for melanomas, leukemias, non-Hodgkin's lymphoma (NHL), and ovarian cancer. Increasing number of ovulatory cycles uninterrupted by pregnancies correlate positively with breast, endometrial, and ovarian cancer risk while pregnancies and breastfeeding lower the risk for these cancers as well as cancers of the colon, lung, pancreas, and NHL. Chronic inflammatory events such as endometriosis or mucosal exposure to talc increase the risk for several types of cancer. Mechanisms so far considered are site specific and do not explain multiple associations. It was propose that most of these events affect cancer immune-surveillance by changing the balance between an effective immune response and immune tolerance of an emerging cancer [242].

Molecular biology

Satellite repeats in heterochromatin are transcribed into noncoding RNAs that have been linked to gene silencing and maintenance of chromosomal integrity. Using digital gene expression analysis, we showed that these transcripts are greatly overexpressed in mouse and human epithelial cancers. In 8 of 10 mouse pancreatic ductal adenocarcinomas (PDACs), pericentromeric satellites accounted for a mean 12 percent (range 1 to 50 %) of all cellular transcripts, a mean 40-fold increase over that in normal tissue. In 15 of 15 human PDACs, alpha satellite transcripts were most abundant and HSATII transcripts were highly specific for cancer. Similar patterns were observed in cancers of the lung, kidney, ovary, colon, and prostate. Derepression of satellite transcripts correlated with overexpression of the long interspersed nuclear element 1 (LINE-1) retrotransposon and with aberrant expression of neuroendocrine-associated genes proximal to LINE-1 insertions. The overexpression of satellite transcripts in cancer may reflect global alterations in heterochromatin silencing and could potentially be useful as a biomarker for cancer detection [243].

The most frequent genetic abnormalities in invasive pancreatic adenocarcinomas are mutational activation of the KRAS oncogene, inactivation of tumour-suppressor genes including CDKN2A, TP53, SMAD4, and BRCA2, widespread chromosomal losses, gene amplifications, and telomere shortening. KRAS mutations and telomere shortening are the earliest known genetic abnormalities recorded, even in low-grade pancreatic intraepithelial neoplasias, and telomere shortening is believed to contribute to chromosomal instability, whereas inactivation of TP53, SMAD4, and BRCA2 happens in advanced pancreatic intraepithelial neoplasias and invasive carcinomas. Genes mutated in a few (<20 %) pancreatic cancers include oncogenes such as BRAF, MYB, AKT2, and EGFR, and tumour-suppressor genes such as MAP2K4, STK11, TGFBR1, TGFBR2, ACVR1B, ACVR2A, FBXW7, and EP300. Structural analysis of mutated genes implicates PIK3CG, DGKA, STK33, TTK, and PRKCG as low-frequency driver mutations [213].

Genetically engineered mouse models targeting some of the genes most commonly altered in human pancreatic cancer have been developed, and several of these recapitulate the human disease and have been used to study mechanisms and investigate therapeutic agents. In addition to the driver genes, epigenetic changes can also alter gene function in pancreatic cancers. Epigenetic dysregulation includes alterations in DNA methylation and histone modifications and non-coding RNAs. Promoter methylation and gene silencing in pancreatic cancers was first reported for the tumour-suppressor gene CDKN2A, of which epigenetic silencing is restricted to neoplasms without genetic inactivation of CDKN2A. Only a few classic tumour-suppressor and DNA-repair genes undergo epigenetic silencing in pancreatic cancers – e.g. MLH1 and CDH1 are methylated in a small proportion of tumours. Many other genes are frequent targets of aberrant methylation and gene silencing in pancreatic cancers, including CDKN1C, RELN, SPARC, TFPI2, and others. Some of the most commonly aberrantly hypermethylated genes in pancreatic neoplasms have been evaluated for their diagnostic or biological relevance. Promoter hypomethylation of overexpressed genes has also been reported for several genes, such as SFN, MSLN, and S100A4, and mucin genes. Alterations in microRNA expression seem to contribute to cancer development and progression. Overexpression of several microRNAs in pancreatic cancers—including miR-21, miR-34, miR-155, and miR-200 is thought to contribute to neoplastic progression. Furthermore, since microRNAs are stable and detectable in human plasma they could be useful diagnostic markers. Genetic and epigenetic alterations of pancreatic cancers probably play a part in tumour aggressiveness and patterns of progression. Major signalling pathways and tumour stromal interactions entailed in pancreatic cancer development and progression [213]:

- The most important pathways include those targeted for genetic and epigenetic alterations – i.e. those that include protein products of KRAS, RB1 and CDKN2A, TP53, and SMAD4 and TGFBR1 genes
- The hedgehog, NOTCH, AKT1-PI3K-MTOR, and BRCA2-PALB2-Fanconi pathways are being investigated as therapeutic targets
- Suspected downstream members of the RAS signaling cascade include RAF, MEK, MAPK (previously known as ERK), STK33, and PLK1
- Melanomas with BRAF mutations respond to BRAF inhibitors and could potentially be of benefit to the few pancreatic cancers (<5 %) that harbour BRAF gene mutations
- Tumor-stromal interactions contribute to oncogenic signalling, including interactions entailing the hedgehog pathway, cyclo-oxygenases, the extracellular matrix protein SPARC, and NFkappaB, among others
- Hedgehog ligands derived from pancreatic cancer cells stimulate non-neoplastic stromal fibroblasts that overexpress the hedgehog pathway receptor called smoothened (SMO), and this paracrine hedgehog signalling stimulates fibroblast-mediated tumour growth; this mechanism of activation of

- the hedgehog pathway is more typical than alterations of the hedgehog pathway in pancreatic cancer cells
- Hedgehog inhibitors effective for patients with basal cell carcinomas and medulloblastomas – cancers with mutational activation of the hedgehog pathway – are undergoing testing in clinical trials in patients with pancreatic cancer
 - The stromal environment could be a physical or pathophysiological barrier preventing chemotherapeutic drugs from reaching pancreatic cancer cells, and elimination of stroma could enhance cancer drug delivery

Molecular evolution of pancreatic cancers has been estimated using somatic mutations as molecular clocks. From this analysis, an initial precursor neoplastic clone will take roughly more than 10 years to evolve into a malignant clone and several additional years for metastatic subclones to emerge from within the primary cancer. Comparison of molecular alterations of a patient's primary pancreatic cancer and metastases reveals not only that almost all the major driver genes are mutated before development of invasive adenocarcinoma but also that genetic instability continues after cancer dissemination, with some genetic heterogeneity arising in different metastases. Although these estimates reflect a range of tumour behaviour in different patients, they indicate that a primary cancer can reside in the pancreas for many years before metastasis, potentially providing opportunities for screening [213].

Tumor microenvironment

Interactions between cancer-associated fibroblasts – the predominant stromal cell type – and neoplastic cells could contribute to tumour initiation, progression, and metastasis. The role of the immune system in pancreatic cancer progression has focused on the potential benefit of inhibition of T regulatory lymphocytes (cells that suppress antitumour immune responses) or use of vaccines – including irradiated genetically modified pancreatic cancer cells or immunostimulatory pancreatic cancer antigens, such as overexpressed (e.g. mesothelin) or mutated proteins. Furthermore, the mechanisms of immune evasion by cancer cells and cancer-associated fibroblasts have been studied. The role of tumour-initiating cells (so-called cancer stem cells) in the development of pancreatic cancer is controversial. Although putative cells have been identified, reconciling the notion of tumour-initiating cells with the clonal selection provided to neoplastic cells by tumorigenic mutations acquired during carcinogenesis is difficult [213].

ABCC4 gene

Pancreatic cancer is a malignant neoplasm of the pancreas that usually has a poor prognosis. The investigation of targets that effectively inhibit pancreatic cancer cell proliferation should provide a fundamental basis for the clinical application of gene therapy. Here, high expression levels of ABCC4 protein in thirty-six pancreatic cancer specimens were quantified using an immunohistochemical assay, and the potential of ABCC4 as a therapeutic target for pancreatic cancer was investigated. Inhibition of ABCC4 expression at the mRNA and protein levels was achieved in Panc-1 and BxPC-3 pancreatic cancer cells infected with a lentivirus expressing an ABCC4 short hairpin RNA (shRNA). The downregulation of ABCC4 expression in Panc-1 and BxPC-3 cells significantly inhibited their proliferation and colony formation in vitro, compared to cells infected with mock control. Moreover, the specific downregulation of ABCC4 led to the accumulation of cells at the G1 phase of the cell cycle. The findings reveal that the ABCC4 gene promotes pancreatic cancer cell growth and represents a promising target for gene therapy in pancreatic cancer [244].

Angiogenesis

Angiogenesis has been associated with disease progression in many solid tumours, however the statement that tumours need angiogenesis to grow, invade and metastasise seems no longer applicable to all tumours or to all tumour subtypes. Prognostic studies in pancreatic cancer are conflicting. In fact, pancreatic cancer has been suggested an example of a tumour in which angiogenesis is less essential for tumour progression. The aim of one study was therefore to measure angiogenesis in two anatomically closely related however prognostically different types of pancreatic cancer, pancreatic head and periampullary cancer, and investigate its relation with outcome. Vessels were stained by CD31 on original paraffin embedded tissue from 206 patients with microscopic radical resection (R0) of pancreatic head (n=98) or periampullary cancer (n=108). Angiogenesis was quantified by microvessel density (MVD) and measured by computerised image analysis of three randomly selected fields and investigated for associations with recurrence free survival (RFS), cancer specific survival (CSS), overall survival (OS) and conventional prognostic factors. MVD was heterogeneous both between and within tumours. A higher MVD was observed in periampullary cancers compared with pancreatic head cancers. Furthermore, MVD was associated with lymph node involvement in pancreatic head, but not in periampullary cancer. Interestingly, MVD was not associated with RFS, CSS or with OS. In conclusion, angiogenesis is higher in periampullary cancer and although associated with nodal involvement in pancreatic head cancer, pancreatic cancer prognosis seems indeed angiogenesis independent [245].

Angiopoietin

Lymphatic metastasis constitutes a critical route of disease dissemination, which limits the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC). As lymphangiogenesis has been implicated in stimulation of lymphatic metastasis by vascular endothelial growth factor-C (VEGF-C) and VEGF-D, it was studied the effect of the angioregulatory growth factor angiopoietin-2 (Ang-2) on PDAC progression. Ang-2 was found to be expressed in transformed cells of human PDAC specimens, with corresponding Tie-2 receptors present on blood and lymphatic endothelium. In vitro in PDAC cells, Ang-2 was subject to autocrine/paracrine TGF-beta stimulation acting on the -61- to +476-bp element of the human Ang-2 promoter. In turn, Ang-2 regulated the expression of genes involved in cell motility and tumor suppression. Orthotopic PDAC xenografts with forced expression of Ang-2, but not Ang-1, displayed increased blood and lymphatic vessel density, and an enhanced rate of lymphatic metastasis (6.7- to 9.1-fold), which was prevented by sequestration of Ang-2 via coexpression of soluble Tie-2. Notably, elevated circulating Ang-2 in patients with PDAC correlated with the extent of lymphatic metastasis. Furthermore, median survival was significantly reduced from 28 to 8 mo in patients with circulating Ang-2 \geq 75th percentile. These findings indicate that Ang-2 participates in the control of lymphatic metastasis, constitutes a noninvasive prognostic biomarker, and may provide an accessible therapeutic target in PDAC [246].

Autophagy

Macroautophagy (autophagy) is a regulated catabolic pathway to degrade cellular organelles and macromolecules. The role of autophagy in cancer is complex and may differ depending on tumor type or context. Here we show that pancreatic cancers have a distinct dependence on autophagy. Pancreatic cancer primary tumors and cell lines show elevated autophagy under basal conditions. Genetic or pharmacologic inhibition of autophagy leads to increased reactive oxygen species, elevated DNA damage, and a metabolic defect leading to decreased mitochondrial oxidative phosphorylation. Together, these ultimately result in significant growth suppression of pancreatic cancer cells in vitro. Most importantly, inhibition

of autophagy by genetic means or chloroquine treatment leads to robust tumor regression and prolonged survival in pancreatic cancer xenografts and genetic mouse models. These results suggest that, unlike in other cancers where autophagy inhibition may synergize with chemotherapy or targeted agents by preventing the up-regulation of autophagy as a reactive survival mechanism, autophagy is actually required for tumorigenic growth of pancreatic cancers *de novo*, and drugs that inactivate this process may have a unique clinical utility in treating pancreatic cancers and other malignancies with a similar dependence on autophagy. As chloroquine and its derivatives are potent inhibitors of autophagy and have been used safely in human patients for decades for a variety of purposes, these results are immediately translatable to the treatment of pancreatic cancer patients, and provide a much needed, novel vantage point of attack [247].

Bcl-2

Apoptosis, or programmed cell death, is an essential part of normal development, homeostasis and immunoregulation. During malignant progression, tumour cells acquire resistance to spontaneous and therapy-induced apoptosis, resulting in uncontrolled growth. The Bcl-2 family of proteins regulates apoptosis by influencing mitochondrial integrity. At least 20 Bcl-2 proteins have been identified in mammals, consisting of proapoptotic factors (for example Bax, Bak, Bok and BH3-only proteins) and antiapoptotic factors (such as Bcl-2, Bcl-XL, Bcl-w and Mcl-1). Two studies suggested that Bcl-2 expression was an independent marker of better survival in PDAC. The seemingly counterintuitive beneficial prognostic effect of Bcl-2 may be related to non-apoptotic functions, such as cell cycle control, or disturbances in the expression of other Bcl-2 family members. The putative role of Bcl-2 in predicting PDAC prognosis remains unclear, as multiple studies have shown no correlation with survival [248].

CD24

The aim of one study was to investigate the role of CD24 in the invasiveness of pancreatic ductal adenocarcinoma (PDAC). It was used 2 human PDAC cell lines containing large numbers of CD24-positive (CD24) cells (>65 %; AsPC-1 cells) or few CD24 cells (<20 %; CFPAC-1 cells). Invasiveness was estimated using the Matrigel invasion assay. The role of CD24 in invasiveness was evaluated using small interference RNA against CD24 mRNA. The invasive ability of CD24 cells collected by cell sorter was higher than that of CD24-negative (CD24) cells. On the other hand, silencing of CD24 decreased the invasive ability of CD24 cells. Importantly, considerable amount of CD24 cells was converted to CD24 cells within 24 hours under *in vitro* culture condition. Transforming growth factor beta1 significantly inhibited this conversion and consequently maintained the high invasiveness of CD24 cells. The data show that CD24 contributes to the invasive ability of PDAC and also suggest that transforming growth factor beta1 may contribute to the invasiveness of PDAC by suppressing the conversion from CD24 cells to CD24 cells at the tumor site [249].

CD34

Microvessel density (MVD) is an established method for quantitating angiogenesis in tumours. A number of endothelial surface markers have been used to examine MVD in PDAC but, among those associated with survival through multivariable analysis, only CD34 was associated with outcome in more than one study. Its prognostic value remains unclear, as other studies have not demonstrated any relationship with survival [248].

Claudin

Pancreatic ductal neoplasms exhibit gastric epithelium-like characteristics. In this study, we evaluated the expression of claudin-18 (CLDN18), a gastric epithelium-associated claudin, in pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and pancreatic ductal adenocarcinomas (PDACs) using immunohistochemistry. It was observed a high level of expression of CLDN18 in PanINs (31/32, 97 %), IPMNs (61/65, 95 %), and MCNs (4/5, 80 %) using ordinary tissue section analysis. Furthermore, it was observed a high level of CLDN18 expression in PDACs (109/156, 70 %) using tissue microarray analysis. However, the normal pancreatic duct or the ductal metaplasia of the acinar cells was not immunoreactive. Comparative analysis of CLDN18 and phenotypic markers in IPMNs revealed that simultaneous expression of CLDN18 and intestinal markers frequently occurred, even in intestinal-type IPMNs. CLDN18 variant 2 mRNA was expressed and was similarly upregulated by phorbol 12-myristate 13-acetate (PMA) treatment in pancreatic cancer cell lines and in a gastric cancer cell line. An inhibitor of pan-PKC (GF109203X) completely suppressed this upregulation in pancreatic cancer cells. These results indicate that CLDN18, a marker for the early carcinogenetic process, is commonly expressed in precursor lesions of PDAC. Activation of the PKC pathway might be involved in CLDN18 expression associated with pancreatic carcinogenesis [250].

Cyclin D1

Cyclin D1 forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is to phosphorylate and inactivate the retinoblastoma protein and promote progression through the G1-S phase of the cell cycle. Mutations, amplification, and overexpression of this gene, which alters cellcycle progression, are observed frequently in a variety of tumors and may contribute to tumorigenesis. Overexpression of cyclin D1 in pancreatic cancers has been reported by a number of authors. In one study, the increased expression of cyclin D1 correlated with poor prognosis, whereas in another study, no such correlation was found. Inhibition of cyclin D1 in pancreatic cancer by small inhibitory RNA not only checks tumor proliferation, but also makes the cells more sensitive toward some therapeutic drugs such as fluoropyrimidines and platinum compounds such as cisplatin [251].

Cyclo-oxygenase 2

Cyclo-oxygenase (COX) 2 is a rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins. It has a multifunctional role in pancreatic cancer development, being implicated in angiogenesis (for example through upregulation of VEGF), proliferation, invasiveness and immunosuppression. Preclinical studies of COX-2 inhibitors are encouraging, and phase II studies using the selective COX-2 inhibitor celecoxib have yielded promising data, although further studies are warranted. Two studies found COX-2 expression to be a prognostic factor independent of conventional clinicopathological parameters, but its prognostic significance remains to be confirmed [248].

Epidermal Growth Factor (EGF)

The epidermal growth factor (EGF) family of receptor tyrosine kinases consists of 4 receptors, EGF-R (ErbB1), ErbB2 (HER 2/Neu), ErbB3, and ErbB4.166,167 The ligands, which are EGF family of growth factors, consist of multiple members, including EGF, TGF- α , amphiregulin, betacellulin, heparinbinding EGF-like growth factor (HB-EGF), epiregulin, and heregulins. After ligand binding, EGF receptors (EGFRs) dimerize, lose their autoinhibition and become active, initiate downstream signaling through Ras-Raf-mitogen-activated protein kinase pathway, thus influencing cell proliferation, differentiation, and survival. Epidermal

growth factor receptors as well as EGFs show an aberrant expression in pancreatic cancers. Overexpression of EGFR in pancreatic cancer has been correlated with advanced disease at presentation, aggressive phenotype, and reduced median survival time. However, in cell lines, EGFR receptor antagonism has been shown to inhibit cell growth. The ligands of the EGF superfamily, such as amphiregulin, betacellulin, HB-EGF-like growth factor, epiregulin, and heregulin, were also shown to be overexpressed in pancreatic cancers and contributed toward pathogenesis. Amphiregulin was associated with advanced clinical stage; HB-EGF and betacellulin contributed toward pancreatic cancer cell growth through aberrant autocrine and paracrine activation; epiregulin had a role in the pathobiology of PDAC, and heregulin-A (but not heregulin-) levels were associated with decreased patient survival. Some EGFRs are overexpressed, whereas others are underexpressed in pancreatic cancer. ErbB2 and ErbB3 are overexpressed, whereas ErbB4 shows decreased expression. Whereas overexpression of ErbB2 and ErbB3 correlated with an advanced disease state and increased invasiveness, ErbB4 expression was associated with a favorable tumor stage. A major partner of EGFR, HER-2 (ErbB2), has also been shown to be overexpressed in pancreatic cancer. Expression of EGFR-related protein (ERRP) showed a negative correlation with the degree of differentiation in pancreatic cancer. Also, low levels of ERRP are associated with poor clinical outcome. Small molecular inhibitors of EGFR, such as erlotinib and gefitinib, act by competing with adenosine-5-triphosphate (ATP) for the intracellular tyrosine kinase domain of the receptor, thus inhibiting EGFR autophosphorylation, and therefore downstream signaling. In a phase 2 clinical trial, adding erlotinib to gemcitabine and bevacizumab showed significantly improved results over gemcitabine monotherapy. In a study, the EGFR inhibitors cetuximab and erlotinib have shown to increase the efficacy of gemcitabine-radiation therapy [251].

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 while five trials reported no statistically significant difference. It was concluded that EGFR expression is a poor prognostic factor for survival in patients with pancreatic cancer [252].

Fibroblast growth factor

Fibroblast growth factor receptors (FGFRs) comprise a family of related but individually distinct tyrosine kinase receptors. They have a similar protein structure, with 3 immunoglobulin-like domains in the extracellular region, a single membrane-spanning segment, and a cytoplasmic tyrosine kinase domain. They are FGFR1, FGFR2, FGFR3, and FGFR4. They are bound by FGFs. Two main types of FGFs studied in cancers are FGF-1 (also known as acidic FGF) and FGF-2 (basic FGF). Both aFGF and bFGF correlate with advanced tumor stage, but only bFGF predicted a shorter patient survival. Basic FGF also correlates to increased invasiveness of pancreatic cancer, giving them tumor growth advantage. Fibroblast growth factor 7 stimulates cell proliferation, in addition to cell migration and invasion, in pancreatic ductal epithelial cells. Another member, FGF10, does not affect cell proliferation in several types of cancer cells, but is involved in migration and invasion in

Pancreatic cancer through interaction with FGFR2, resulting in a poor prognosis. In fact, an increased expression of FGF receptor is correlated with the extent of malignancy and postoperative survival in PDAC. Measuring the intratumoral levels of bFGF will tell whether the disease is resistant to paclitaxel and thereby help modify treatment regimens.²³⁴ Fibroblast growth factor-binding protein, FGF-BP1, is a secreted chaperone molecule, which enhances the biological functions of FGFs by releasing FGFs from the ECM. This secreted FGF-BP1 can be an indicator of early stages of pancreatic and might be used as a possible serum maker for high-risk premalignant lesions [251].

GLUT-4

GLUT-1 has been found to have an important role in the upregulation of various cellular pathways and implicated in neoplastic transformation correlating with biological behavior in malignancies. However, literature regarding the significance of GLUT-1 expression in pancreatic neoplasia has been limited and controversial. Immunohistochemical expression of GLUT-1 was tested in a variety of pancreatic neoplasia including ductal adenocarcinomas (DAs), pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and serous cystadenomas. There was a progressive increase in the expression of GLUT-1 from low- to higher-grade dysplastic lesions: All higher-grade PanINs/IPMNs (the ones with moderate/high-grade dysplasia) revealed noticeable GLUT-1 expression. Among the 94 DAs analyzed, there were minimal/moderate expression in 46 and significant expression in 24 DAs. However, all 4 clear-cell variants of DAs revealed significant GLUT-1 immunolabeling, as did areas of clear-cell change seen in other DAs. Moreover, all 12 serous cystadenomas expressed significant GLUT-1. GLUT-1 expression was also directly correlated with DA histological grade and tumor size. It was concluded that GLUT-1 may give rise to the distinctive clear-cell appearance of these tumors by inducing the accumulation of glycogen in the cytoplasm. Additionally, because GLUT-1 expression was related to histological grade and tumor size of DA, further studies are warranted to investigate the association of GLUT-1 with prognosis and tumor progression [253].

Heparanase

Pancreatic cancer is characterized by very low survival rates because of high intrinsic resistance to conventional therapies. Ionizing radiation (IR)-enhanced tumor invasiveness is emerging as one mechanism responsible for the limited benefit of radiotherapy in pancreatic cancer. In one study, it was established the role of heparanase – the only known mammalian endoglycosidase that cleaves heparan sulfate-in modulating the response of pancreatic cancer to radiotherapy. It was found that clinically relevant doses of IR augment the invasive capability of pancreatic carcinoma cells in vitro and in vivo by upregulating heparanase. Changes in the levels of the transcription factor Egr-1 occurred in pancreatic cancer cells following radiation, underlying the stimulatory effect of IR on heparanase expression. Importantly, the specific heparanase inhibitor SST0001 abolished IR-enhanced invasiveness of pancreatic carcinoma cells in vitro, whereas combined treatment with SST0001 and IR, but not IR alone, attenuated the spread of orthotopic pancreatic tumors in vivo. Taken together, our results suggest that combining radiotherapy with heparanase inhibition is an effective strategy to prevent tumor resistance and dissemination, observed in many IR-treated pancreatic cancer patients. Further, the molecular mechanism underlying heparanase upregulation in pancreatic cancer that we identified in response to IR may help identify patients in which radiotherapeutic intervention may confer increased risk of metastatic spread, where antiheparanase therapy may be particularly beneficial [254].

Human equilibrative nucleoside transporter 1

Gemcitabine, a pyrimidine nucleoside analogue, is commonly used as the standard chemotherapeutic agent for PDAC. However, pancreatic cancer cells exhibit high levels of inherent and acquired chemoresistance, limiting its clinical impact. It has been reported that tissue mRNA levels of the human equilibrative nucleoside transporter (hENT) 1, which mediates cellular entry of gemcitabine, correlated with survival. Two subsequent IHC studies demonstrated that hENT1 was an independent predictive marker for gemcitabine-related outcome. In the Radiation Therapy Oncology Group (RTOG) 9704 study, a total of 538 patients with resected PDAC were randomized to either 5-fluorouracil (5-FU) or gemcitabine. In the group receiving 5-FU, hENT1 expression was not associated with survival. There was, however, a correlation between hENT1 levels and overall and disease-free survival in the group given gemcitabine. Expression of hENT1 holds promise as a predictive factor to identify those likely to benefit from gemcitabine-based chemotherapy [248].

IkappaB kinase

IkappaB kinase (IKKepsilon) is a serine/threonine protein kinase that belongs to the IKK kinase family. Recent studies have shown that IKKepsilon functions as a breast and ovarian cancer oncogene. It was demonstrated frequent overexpression of IKKepsilon in pancreatic ductal adenocarcinoma (PDA). It was immunohistochemically evaluated 78 PDAs using the avidin-biotin-peroxidase method and the anti-IKKepsilon rabbit polyclonal antibody. Elevated IKKepsilon reactivity (immunohistochemical score, 4-9) was observed in 64 percent of PDAs (50/78), but in 0 percent of nonneoplastic pancreatic ductal epithelium (0/113). Kaplan-Meier analysis of overall survival revealed that patients with high IKKepsilon-immunohistochemical scores (4-9) had significantly shorter survival than did patients with low IKKepsilon immunohistochemical scores (0-3) independent of tumor stage or grade. These data indicate that deregulation of IKKepsilon is a common event in PDA and might have an important role in the pathogenesis of this deadly disease. In addition, IKKepsilon could serve as a prognostic marker and potential therapeutic target for PDA intervention [255].

Ki-67

Normal cells require mitogenic growth signals to go from a quiescent to an active proliferative state. Tumour cells are less dependent on external growth stimuli and are self-sufficient. Ki-67 is a nuclear antigen present in proliferating cells during all active phases of the cell cycle (G1, S, G2 and M), but not during the quiescent phase (G0). Several small studies have identified proliferation index as measured by Ki-67 as an independent predictor of survival in pancreatic carcinoma. In the largest of these studies, the prognostic value of Ki-67 index, p21, p27 and p53 was examined in 77 patients with pancreatic cancer. Using multivariable analysis, only a Ki-67 index greater than 5 percent showed prognostic significance. Other studies have found no association between Ki-67 and survival in pancreatic cancer [248].

KLF4

The transcription factor Krüppel-like factor 4 (KLF4) may act both as an oncogene and a tumor suppressor in a tissue-dependent manner, and further studies on its role in pancreatic ductal adenocarcinoma (PDAC) progression and clinical outcome are warranted. Therefore, it was investigated the loss of heterozygosity (LOH) in the 9q22.3-32 region and loss of KLF4 gene expression in epithelial cells from 35 PDAC, 6 pancreatic intraductal neoplasias (PanINs) and 6 normal ducts, isolated by laser microdissection, as well as their correlation with overall survival (OS) in patients treated with gemcitabine in the adjuvant setting. LOH was evaluated with 4 microsatellite markers and in situ hybridization, while KLF4 expression was studied by reverse transcription-PCR and immunohistochemistry. LOH in at least 1 locus

was observed in 25 of 35 PDAC cases and in 5 of 6 PanINs, respectively. In particular, the loss of the D9S105 marker was present in 47 percent of PDAC and 83 percent of PanINs, becoming the most deleted marker, while no LOH in D9S105 was observed in normal Wirsung pancreatic duct. Lack of KLF4 mRNA expression was significantly associated with genomic deletion flanking KLF4 in PDAC and in PanINs (with LOH of D9S105), low-grade PDAC-associated PanIN, lack of KLF4 protein expression, and shorter OS. These results strongly suggest a relationship between D9S105 deletion and downregulation of KLF4 gene expression as an early event in PDAC progression, as well as a possible role of KLF4 as a prognostic biomarker in gemcitabine-treated patients [256].

K-ras

More clinically meaningful diagnostic tests are needed in exocrine pancreatic cancer (EPC). K-ras mutations are the most frequently acquired genetic alteration in EPC. It was analysed the diagnostic utility of detecting K-ras mutations through a systematic analysis of the literature. It was searched PubMed using suitable medical subject headings and text words. Original research articles that evaluated the diagnostic accuracy of detecting K-ras mutations for diagnosis of EPC were selected. Two investigators independently extracted data from each study regarding the methodology used, the methodological quality of the study, the diagnostic accuracy reported and the authors' conclusions about clinical applicability of the test. Combined estimates for the sensitivity and specificity of K-ras were determined using bivariate meta-analysis; heterogeneity was explored using meta-regression. It was assessed 34 studies from 30 published articles. The research reports were prone to numerous methodological biases and often lacked vital information for assessing external validity. The sensitivity of detecting K-ras status ranged from 0 percent through 100 percent, and the specificity from 58 percent through 100 percent. Diagnostic accuracy was highest when cytohistological samples were used: sensitivity and specificity were 77 percent and 92 percent, respectively. Studies conducted in a clinically relevant population observed lower accuracy than case-control designs (68 % vs 83 %). Because of the numerous methodological limitations of studies, the utility of analysing K-ras mutations for the diagnosis of EPC remains unknown. Flaws in diagnostic biomarkers with well-established biological properties, as K-ras, become even more relevant when the promises of "personalized medicine" are pondered [257].

In the classic PanIN model of tumor progression, K-ras mutation is one of the earliest genetic events to occur, which predisposes cells toward further mutations, resulting in tumor development. K-ras mutation is a critical event in the development of pancreatic cancer. It is the most prevalent type of mutation present in PDAC, occurring in 80 to 100 percent of cases. Its mutation is the first known genetic alteration in PDAC, occurring sporadically in normal pancreatic tissue, and is detected in 30 percent of early neoplasms, with the frequency rising to nearly 100 percent in advanced PDAC. The point mutation of K-ras in PDAC typically occurs in codon 12 (GGT to GAT, GTT, or rarely to CGT), resulting in the substitution of glycine with aspartate, valine, or arginine, respectively. Because K-ras is a GTPase and requires GTPase-activating proteins for its downstream effector functions, this point mutation tends to constitutively activate K-ras oncogene, making it independent of growth factor stimulation. The result is an uncontrolled mediation of a variety of cellular functions including unchecked proliferation and survival. Mutated K-ras also plays a role in angiogenesis through CXCR chemokines and vascular endothelial growth factor (VEGF). Different studies have demonstrated K-ras to be indispensable for maintenance of advanced PDAC. K-ras mutations also contribute toward other pancreatic conditions, such as chronic pancreatitis and cystic papillary carcinoma. The fact that chronic pancreatitis predisposes toward PDAC, and a recent report demonstrating K-ras mutations to contribute toward PDAC development only in combination with nongenetic tissue damage (as in chronic pancreatitis), suggests that the link between the two may be a mutated K-ras gene. Major K-ras downstream pathways, such as Raf-MAPK pathway, phosphoinositide 3-kinase pathway,

and nuclear factor κ B (NF- κ B), were inhibited at different levels using different methods. Mutated K-ras abrogates p53 function by stabilizing Snail, which directly binds to the DNA-binding domain of p53, thereby diminishing its tumor suppressive functions. Elimination of Snail by siRNA or inhibition of Snail-p53 binding by chemicals enhanced the expression as well as transcriptional activity of p53 in K-rasYmutated cells. Inhibition of proteolysis by a Kras-dependent E3 ubiquitin ligase (SIAH) resulted in the formation of fibroblasts and abolished tumor growth of human pancreatic cancer cells in soft agar as well as in athymic nude mice. In K-rasYmutated cells, after the elimination of p53-Snail, while p53 gets resorbed, the cosecreted Snail resists endocytosis and remains in the culture. Thus, detection of anti-Snail antibodies in blood serum can be used as a diagnostic tool for pancreatic cancer. Evaluation of K-ras mutations in pancreatic juice can provide a tool for screening and early detection of pancreatic cancer. A big leap forward in the clinical use of K-ras is that circulating K-ras in the peripheral blood of patients with locally advanced pancreatic cancer has been taken as a potential biomarker for the response to combined radiotherapy and chemotherapy in a phase 1 clinical trial [251].

Matrix metalloproteinases

Proteins of the MMP family are involved in the breakdown of ECM in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. Matrix metalloproteinases are collectively able to degrade virtually all ECM components. In cancer, special emphasis was initially placed on the degradation of type IV collagen, a major protein component of basement membranes by MMP-2 and MMP-9. Matrix metalloproteinase-induced release from the cell surface (shedding) of HB-EGF, insulinlike growth factor, and FGF enhances cell proliferation. On the other hand, release and activation of ECM sequestered TGF- α by MMPs can lead to inhibition of cell proliferation. There are several different MMPs, of which the most commonly studied in pancreatic cancer are MMP-2, MMP-7, and MMP-9. Matrix metalloproteinase 7 was mainly expressed in the cytoplasm of acinar or ductal cells as against intracellular expression of proMMP-7. Matrix metalloproteinase 9 is detected both in cells and matrix, cancer and stromal cells being the major source of matrix MMP-9 in pancreatic ductal carcinoma tissues. Matrix metalloproteinase 2 can be detected both in the foci of cells in the zone of tumor growth, as well as in the ECM (stroma) of tumors. The overexpression of MMP-7 was significantly associated with metastasis and 1-year survival in PC, but not with tumor size, extent of differentiation, and cell proliferation. Matrix metalloproteinase 7 showed stronger expression at the invasive front, as compared with the center of pancreatic tumors, and was found to be involved in cell dissociation and the subsequent invasion of PC cells, by forming a positive feedback loop with activation of the EGFR-mediated MEK-ERK signaling pathway. The coexpression of MMP-2 and MMP-9 is an unfavorable prognostic sign. In vivo testing revealed that MMP inhibitors are useful tools in anticancer therapy, reducing tumor size and invasion even without direct effects on cell survival [248].

MSH2

The objective of one study was to describe a novel MSH2 missense alteration cosegregating with pancreatic cancer. The method used was an observational study of a kindred in which a novel MSH2 missense alteration was identified. It was reported a family in which a MSH2 P349L missense alteration is cosegregating with pancreatic cancers among 3 nonsmoking first-degree relatives. Lynch syndrome-related tumors from individuals carrying this alteration consistently showed loss of immunohistochemical expression of MSH2, and in silico analyses support the interpretation of this DNA alteration as likely pathogenic. The MSH2 P349L may increase the risk for pancreatic cancer beyond the usual mutations in DNA

mismatch repair genes; however, studies of additional families with the identical missense alteration are needed to confirm this initial impression [258].

Mucins

Alterations in mucin (MUC) glycosylation and expression have been described in cancer. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can provide material for molecular biology analysis. This study assessed the feasibility of evaluating MUC expression from material obtained by EUS-FNA and studied the profile of MUC expression in benign and malignant pancreatic lesions. A total of 90 patients with solid or cystic pancreatic lesions underwent FNA. The aspirated material was used for cytological analysis and RNA extraction to assess the expression pattern of MUCs by reverse transcription-PCR with primers specific for the MUC1, MUC2, MUC3, MUC4, MUC5A, MUC5B, MUC6, and MUC7 genes. RNA extraction was successful in 81 percent of the biopsies. The prevalences of MUC1, MUC2, MUC4, and MUC7 in ductal adenocarcinoma were 58, 51, 20, and 73 percent, respectively. Fifty percent of benign lesions and neuroendocrine tumors (NETs), and 63 percent of intraductal papillary mucinous neoplasms (IPMNs) were positive for MUC1. Twenty-five percent of benign lesions, 86 percent of NETs, and 47 percent of IPMNs were positive for MUC2. Of NETs, 50 percent were positive for MUC1, and 14 percent were positive for MUC7. None of the benign lesions or NETs expressed MUC4. MUC7 expression was highly significant for adenocarcinoma and borderline for IPMN. MUC7 was expressed in 38 percent of chronic pancreatitis cases. It was concluded that RNA can be extracted from samples obtained under EUS-FNA. MUC7 could serve as a potential biological marker to identify malignant lesions, especially pancreatic adenocarcinoma [259].

Pigment epithelium-derived factor

Pigment epithelium-derived factor (PEDF) is a noninhibitory member of the serine protease inhibitor gene family with neuroprotective, neuroproliferative, and anti-angiogenic functions. Its role in pancreatic fibrosis and neuropathy is unknown. The expression and localization of PEDF were assessed by quantitative real-time (RT)-PCR, immunohistochemistry, and quantitative image analysis and correlated with neural and microvessel densities (MVDs) in the normal pancreas (n=20) and pancreatic cancer (n=55). Primary human pancreatic stellate cells (PSCs), mouse neuroblastoma, and human Schwann cells were used for functional experiments. The effect of hypoxia on PEDF production in cancer cell lines and immortalized pancreatic ductal epithelial cells was assessed by quantitative RT-PCR and enzyme-linked immunosorbent assay. The effect of recombinant PEDF on PSCs was assessed by immunoblot analysis. PEDF expression was homogeneous in epithelial cells of the normal pancreas where some acinar cells consistently displayed stronger staining. A higher expression was found in tubular complexes, PanIN lesions, and inflammatory cells in pancreatic cancer. Cancer cells expressed various levels of PEDF. In cancer cell lines and in human immortalized pancreatic ductal epithelial cells, hypoxia increased PEDF mRNA up to 132-fold. Higher expression of PEDF in cancer cells was significantly correlated with better patient survival (median survival 22 months vs 18 months), increased neuropathy, increased PSC activity, and extracellular matrix protein production. PEDF increases PSC activity, thereby contributing to the desmoplasia of pancreatic cancer. PSC overactivation likely leads to periacinar fibrosis and degeneration of fine acinar innervation. Increased focal PEDF expression in cancer cells correlates with neuropathic changes and better patient survival [260].

S100A4

Metastasis is a complex, multistep process, involving local invasion, intravasation, extravasation and colonization at distant sites. S100A4, a member of the S100 family of Ca²⁺-

binding proteins, plays an important role in metastatic progression including regulation of cancer cell motility via interactions with myosin-IIa166, cell cycle progression, angiogenesis, and chemoresistance. A correlation between S100A4 expression levels and metastasis has been suggested in several human cancers, including breast, oesophageal, lung, pancreatic, colorectal, prostate and gastric tumours. Two studies found it to be an independent marker of adverse outcome in PDAC. Recent in vitro data indicate that knockdown of S100A4 suppresses cell proliferation and the invasiveness of PDAC cells. These observations suggest that S100A4 could potentially serve as a novel prognostic marker and a target for therapeutic intervention in patients with PDAC [248].

Smad4

Smad4 is a member of the Smad family of signal transduction proteins. Smad proteins are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to transforming growth factor A (TGF-A) signaling. Smad4 is a common mediator, which forms a heteromeric complex with phosphorylated Smad2 or Smad3 and translocates to the nucleus, where Smad4-Smad2/3 along with other cofactors bring about transcription. Heteromeric Smad4 complex mainly transcribes cell-cycle regulatory genes such as p53, p15, p21, and p27. Although lost in other cancers too, loss of Smad4 is more sensitive and specific to PDAC. It is inactivated in 55 percent of pancreatic cancers either by deletion of both alleles (35 %) or by intragenic mutation in 1 allele coupled with the loss of the other alleles (20 %). Deletion of Smad4 occurs at a later stage of PanIN. Loss of Smad4 protein expression is highly correlated with the presence of widespread metastasis but not with locally destructive tumors. Involvement of K-ras/ERK pathway, PTEN and RON, respectively, is implicated in the gain of metastatic potential of pancreatic cancers in the absence of Smad4. Smad4 is thought to be dispensable for normal pancreas but critical for the progression of tumors with mutated K-ras gene. SMAD4 gene inactivation is associated with poorer prognosis in patients with surgically resected PDAC. Determination of Smad4 status at initial diagnosis may be of value in determining the stage and metastatic status of disease and will help in stratifying patients into treatment regimens accordingly. Success with SMAD4 gene transfection of Smad4-deficient cells lines has been variable [251].

Somatostatin

Somatostatin (SST) inhibited cell proliferation and negatively regulated the release of growth hormones by means of specific receptors (SSTR). Genetic variation in SSTR had been associated with risk of human cancers but had never been investigated in pancreatic cancer. In this retrospective study the SSTR5 gene in paired tumor and blood samples from 33 pancreatic adenocarcinoma patients using the Sanger method were sequenced. Three single nucleotide polymorphisms (SNPs) in samples from 863 patients with pancreatic ductal adenocarcinoma and 876 healthy controls using the TaqMan method were analyzed. The associations between gene polymorphisms and pancreatic cancer risk and survival were analyzed by multivariate logistic regression and Cox proportional hazard models, respectively. No somatic mutations were identified, but 3 nonsynonymous SSTR5 SNPs (P109S, L48M, and P335L) in pancreatic tumors were identified. The SSTR5 P109S variant allele was associated with a 1.62-fold increased risk of pancreatic cancer (95 % confidence interval 1.08 to 2.43). Furthermore, the SSTR5 L48M AC variant and smoking had a joint effect on pancreatic cancer risk. The odds ratios were 0.58, 1.49, and 2.27 for the variant genotype alone, smoking alone, and both factors, respectively, compared with no factors. Finally, SSTR5 P335L CC and P109S CC combined were associated with lower overall survival durations in patients with resectable disease. These data suggest that SSTR5 genetic variants play a role in pancreatic cancer development and progression [261].

Sonic hedgehog

To conduct a systematic review of the role that the hedgehog signaling pathway has in pancreatic cancer tumorigenesis a PubMed search (2000-2010) and literature based references was made. Firstly, in 2009 a genetic analysis of pancreatic cancers found that a core set of 12 cellular signaling pathways including hedgehog were genetically altered in 67-100 percent of cases. Secondly, in vitro and in vivo studies of treatment with cyclopamine (a naturally occurring antagonist of the hedgehog signaling pathway component; smoothed) has shown that inhibition of hedgehog can abrogate pancreatic cancer metastasis. Thirdly, experimental evidence has demonstrated that sonic hedgehog (Shh) is correlated with desmoplasia in pancreatic cancer. This is important because targeting the Shh pathway potentially may facilitate chemotherapeutic drug delivery as pancreatic cancers tend to have a dense fibrotic stroma that extrinsically compresses the tumor vasculature leading to a hypoperfusing intratumoral circulation. It is probable that patients with locally advanced pancreatic cancer will derive the greatest benefit from treatment with smoothed antagonists. Fourthly, it has been found that ligand dependent activation by hedgehog occurs in the tumor stromal microenvironment in pancreatic cancer, a paracrine effect on tumorigenesis. Finally, in pancreatic cancer, cells with the CD44+CD24+ESA+ immunophenotype select a population enriched for cancer initiating stem cells. Shh is increased 46-fold in CD44+CD24+ESA+ cells compared with normal pancreatic epithelial cells. Medications that destruct pancreatic cancer initiating stem cells are a potentially novel strategy in cancer treatment. It was concluded that aberrant hedgehog signaling occurs in pancreatic cancer tumorigenesis and therapeutics that target the transmembrane receptor Smoothed abrogate hedgehog signaling and may improve the outcomes of patients with pancreatic cancer [262].

Survivin

Survivin is a member of the inhibitor of apoptosis protein family. It was originally described as an inhibitor of caspases. Recent studies have uncovered additional complex biological roles in controlling the fate of the cell. Different prognostic roles for nuclear and cytoplasmic survivin expression have been demonstrated. Prognostic data for expression of survivin are conflicting. Two studies have identified cytoplasmic survivin as an independent prognostic marker, but four found no such association [248].

Transforming growth factor A

Transforming growth factor A is a member of the TGF-A superfamily, which is a collection of growth factors that exert a wide range of biological effects, including cell growth and differentiation, angiogenesis, cell invasion, extracellular matrix (ECM) composition, local immune function, and apoptosis. Transforming growth factor A physiologically functions as a negative regulator of epithelial cell growth and ECM composition. There are 3 mammalian TGF-A isoforms that bind to the type II TGF-A receptor (TARII), which then heterodimerizes with the TARI, thereby affecting downstream signaling via the Smad family of proteins. All 3 mammalian TGF-A isoforms are overexpressed in PDAC, and their overexpression has been correlated with decreased patient survival. Also, cancer cells lose the ability to respond to the growth inhibitory signals of TGF-A. Sometimes, an indirect inhibition of TGF-A signaling can occur because of inactivating mutations in the Smad4 gene or an up-regulation of the inhibitory Smad6 and Smad7 genes. Transforming growth factor A deregulation, besides losing its ability to bring about growth suppression, promotes metastasis and brings about epithelial mesenchymal transition. A compensatory down-regulation of Smad4 can counteract TGFAYinduced cell cycle arrest and migration but not epithelial-mesenchymal transition, which results in increased motility and invasion. Some Smad4-independent TGF-A pathways contribute toward its metastatic role in transformed cells. One such Smad4-

independent pathway is TGF- α -induced transcriptional down-regulation of tumor suppressor PTEN by oncogenic K-ras. Transforming growth factor A may also suppress PTEN through NF- κ B activation and enhance cell motility and invasiveness in a Smad4-independent manner. Loss of Smad4 leading to aberrant activation of Stat3 also contributes to the switching of TGF- α from a tumor-suppressive to a tumor-promoting pathway in pancreatic cancer [251].

Transforming growth factor beta

Transforming growth factor (TGF) β 1 is a polypeptide growth factor implicated in various cellular processes, including cell proliferation, embryogenesis, motility, differentiation, angiogenesis, apoptosis, immunosuppression and extracellular matrix remodelling. The growth suppressive activities of TGF- β dominate in normal adult tissues. In pathological conditions, various cell types lose their ability to respond to TGF- β with growth arrest and cell death, and TGF- β can present with pro-oncogenic properties in cancer. Inactivation or loss of the TGF- β signalling effector SMAD4 (DPC4) is found in approximately 50 percent of pancreatic cancers, resulting in aberrant TGF- β signalling. TGF- β can act both as a tumour suppressor and as a tumour promoter in pancreatic cancer, depending on tumour stage and cellular context. In one study, TGF- β 1 expression was an independent prognostic marker for prolonged survival. A similar conclusion was reached in a more recent study, although other studies have not been able to confirm these findings [248].

Vascular endothelial growth factor

Neovascularization must occur for a solid tumour to exceed 1 mm³ in size. Angiogenesis is a dynamic process regulated by both proangiogenic and antiangiogenic molecules. Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis. The VEGF-related family members include VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor (PlGF) 1 and PlGF-2, along with the receptors VEGFR-1, VEGFR-2 and VEGFR-3. VEGF-targeted therapy has been approved in the treatment of several solid tumours, including glioblastoma and colorectal, renal, breast and non-small cell lung carcinoma. Expression of VEGF has been reported to be present in more than 90 percent of PDAC tumours, and it has been studied extensively for its potential prognostic significance. So far, nine of 18 studies have reported an association between VEGF protein expression and a shorter survival for patients with pancreatic carcinoma, with three studies identifying VEGF as an independent prognostic marker [248].

Vascular endothelial growth factor is a glycosylated mitogen that binds to receptors and induces angiogenesis via a direct effect on endothelial cells. Vascular endothelial growth factor receptor 1 (VEGFR-1 or Flt-1), VEGFR-2, and VEGFR-3 have been identified and extensively studied with regard to angiogenesis. One study has correlated VEGF expression with significantly poorer prognosis in pancreatic cancer. Two other studies, however, could not find any correlation between VEGF and prognosis, but proposed that VEGF alone or along with Cx43 might be of value in judging the metastatic potential of disease and hence prove to be a good diagnostic tool. Because VEGFR-1 is ubiquitously expressed in pancreatic cancer cell lines, overexpression of VEGF in tumors may activate tumor cells bearing VEGFR-1 via an autocrine pathway. Besides influencing tumor cell invasion and migration, it plays a role in tumor progression in pancreatic cancer through the induction of EMT. VEGF-D plays a pivotal role in stimulating lymphangiogenesis and lymphatic metastasis in PDAC. Bevacizumab (Avastin; Roche, Basel, Switzerland) is a recombinant, humanized anti-VEGF monoclonal antibody that binds to soluble VEGF, preventing its receptor binding and thus inhibiting endothelial cell proliferation and blood vessel formation. Preclinical and clinical studies have shown that bevacizumab alone or in combination with a cytotoxic agent decreases tumor growth and increases median survival time and tumor progression [251].

Vimentin

Tumour epithelial vimentin expression is a marker of mesenchymal differentiation and may be a useful marker of carcinomas with more aggressive behaviour. The aim of one study was to determine the extent and prognostic significance of vimentin expression in pancreatic ductal adenocarcinomas. Vimentin expression was detected by immunohistochemistry on tissue microarrays of surgically resected pancreatic ductal adenocarcinomas from 387 patients. The percentage of vimentin-immunolabelled neoplastic cells was correlated with outcome and with clinico-pathological factors using the Kaplan-Meier method and Cox multivariate survival models. In all, 45 percent of primary pancreatic adenocarcinomas contained neoplastic cells that expressed vimentin, and in 28 percent of the cancers >10 percent of cells expressed vimentin. Vimentin expression was correlated with poor histological differentiation. By both uni- and multivariate survival analysis, neoplastic vimentin expression (HR 1.52, 95 % confidence interval 1.14 to 2.04) was an indicator of a shorter postsurgical survival independent of other clinico-pathological variables. The presence of vimentin-expressing tumour epithelial cells in surgically resected pancreatic adenocarcinomas independently predicted a shorter postsurgical survival [263].

Genetics

The last decade has seen significant progress in understanding the molecular biology of pancreatic adenocarcinoma. There is now an urgent need to translate these molecular techniques to clinical practice in order to improve diagnosis and prediction of response to treatment. The objectives of this study are to utilise poly(A) RT-PCR to measure expression levels of diagnostic Indicator genes, selected from microarray studies, of RNA from intraoperatively sampled pancreatic ductal juice and to correlate these expression levels with those in matched pancreatic tissue resection samples. Intraoperative sampling of pancreatic juice and collection of matched tissue samples was undertaken in patients undergoing pancreaticoduodenectomy for suspected tumour. RNA was isolated and poly(A) PCR and real-time PCR used to measure expression levels of 30 genes. Of the 30 Indicator genes measured, just one, ANXA1, showed a significant correlation of expression level between pancreatic juice and tissue samples, whereas three genes, IGFBP3, PSCA, and SPINK1, showed significantly different expression between cancerous and benign pancreatic tissue samples. These results demonstrate that RNA analysis of pancreatic juice is feasible using the poly(A) cDNA technique, that correlation of gene expression exists between pancreatic juice and tissue for very few genes and that gene expression profiling can distinguish between benign and malignant pancreatic tissue. This indicates possible use of the technique for measurement of Indicator genes in pancreatic tissue for diagnosis of pancreatic cancer from very small tissue samples [264].

Substantial progress has been made in our understanding of the biology of pancreatic cancer, and advances in patients' management have also taken place. Evidence is beginning to show that screening first-degree relatives of individuals with several family members affected by pancreatic cancer can identify non-invasive precursors of this malignant disease. Familial pancreatic cancer is defined in most studies as families in which a pair of first degree relatives have been diagnosed with pancreatic tumours. Prospective analysis of families with this malignant disease shows that first-degree relatives of individuals with familial pancreatic cancer have a ninefold increased risk of this neoplasm over the general population. This risk rises to 32-fold greater in kindreds with three or more first-degree relatives with pancreatic cancer. Furthermore, evidence indicates that the risk of pancreatic cancer is modestly increased in first-degree relatives of patients with sporadic pancreatic cancer compared with the general population. Of kindreds with familial pancreatic cancer, risk is highest in those with a case of young-onset pancreatic cancer (age <50 years) in the family compared with

those without a young-onset case. Patients with familial pancreatic cancer also have more precancerous lesions than those with sporadic pancreatic tumours and have an augmented risk of developing extra-pancreatic cancers. Inherited susceptibility to pancreatic cancer:

- germline mutations in BRCA2, PALB2, CDKN2A, STK11, and PRSS1 genes, and Lynch syndrome, are associated with a substantially increased risk of pancreatic cancer
- germline BRCA2 gene mutations account for the highest proportion of known causes of inherited pancreatic cancer
- germline BRCA2 gene mutations have been identified in 5-17 % of families with familial pancreatic cancer
- some patients with pancreatic cancer and a germline BRCA2 gene mutation do not have a relevant family history of breast, ovarian, or pancreatic cancer to raise suspicion that they carry such mutations
- germline BRCA2 gene mutations are associated with 10 % of unselected, apparently sporadic, pancreatic cancers in the Ashkenazi Jewish population
- PALB2 (partner and localiser of BRCA2) has been identified as a pancreatic cancer susceptibility gene
- germline PALB2 mutations are recorded in up to 3 % of patients with familial pancreatic cancer
- protein products of BRCA2 and PALB2 function in the Fanconi DNA repair pathway
- germline mutations in other genes of the Fanconi DNA repair pathway (FANCC, FANCG) are rare
- identification of cancers with inactivation of the BRCA2-PALB2-Fanconi DNA repair pathway has therapeutic implications, since these cancers are highly sensitive to PARP inhibitors and alkylating agents
- germline CDKN2A gene mutations are noted generally in families with familial atypical multiple-mole melanoma, germline STK11 mutations in patients with Peutz-Jeghers syndrome, and germline PRSS1 mutations in people with hereditary pancreatitis
- patients with hereditary non-polyposis colon cancer (Lynch syndrome) have a modest increased risk of developing pancreatic cancer
- findings of genome-wide association studies showed an association between non-O blood group and pancreatic cancer,3 confirming data of prospective cohort studies
- other variants have been implicated as risk factors for pancreatic cancer by findings of genome-wide association studies, including the telomerase subunit locus TERT

Once an individual's cancer predisposition gene is identified, family members can undergo genetic testing and, if appropriate, cancer screening and chemoprevention. However, germline genetic testing of patients with pancreatic cancer is probably underused, in large part because of a failure to recognise from the family history the possibility of a familial cancer syndrome. Usually, kindreds affected by pancreatic cancer who have mutated susceptibility genes do not manifest a high penetrance of pancreatic cancer. For this reason, and because much of the inherited sensitivity to pancreatic cancer remains unexplained, consensus guidelines have not been established to steer genetic testing for inherited susceptibility to pancreatic cancer. BRCA2 gene testing should be considered – after appropriate genetic counseling – for patients of Jewish ethnic origin, those with a strong family history of breast cancer, or individuals with many first-degree relatives with pancreatic cancer; germline CDKN2A testing should be done if there is a family history of familial atypical multiple-mole melanoma. Even without genetic testing, obtaining a detailed family history of cancer can be used for prediction of clinical risk, and mendelian risk-prediction

programmes have been evaluated for their use for individuals with familial pancreatic cancer [213].

The progression model of pancreatic ductal adenocarcinoma (PDAC), distinguishing 4 pancreatic intraepithelial neoplasia (PanIN) grades (PanIN-1A to PanIN-3), is associated with multiple genetic alterations. During early genetic events such as activating point mutations in K-ras oncogene and overexpression of HER-2/neu gene product, pancreatic duct lesions show minimal cytological and architectural atypia. Inactivation of the p16 tumor suppressor gene appears to occur at a later stage followed by the loss of p53, SMAD4, and BRCA2 tumor suppressor genes. According to this model and various studies since then, the initial genetic changes serve as a trigger for subsequent molecular and genetic events to occur, and this sequential acquisition of mutations results in progression of the disease. Therefore, a better understanding of the biology of PDAC would provide insights into the treatment of this disease [251].

Clonal nature of cancer

Cancers frequently arise as a result of an acquired genomic instability and the subsequent clonal evolution of neoplastic cells with variable patterns of genetic aberrations. Thus, the presence and behaviors of distinct clonal populations in each patient's tumor may underlie multiple clinical phenotypes in cancers. Large-scale investigations of cancer genomes are expected to lead to the discovery of common disease elements, including recurring genomic aberrations that can guide the development of broadly applicable diagnostics and therapeutics. Therefore, there is a need for a unique approach (i.e. not reliant on prevalence-based studies) to identify and interpret sets of selected aberrations and define the clinical dependencies that arise in complex, highly variable carcinoma genomes in patients in vivo. It was applied DNA content-based flow sorting to identify and isolate the nuclei of clonal populations from tumor biopsies, which was coupled with array CGH and targeted resequencing. Flow cytometry-based cell sorters can select, objectively measure, and sort individual particles such as cells or nuclei using desired features objectively defined by fluorescent and light-scattering parameters in a flow stream. Recent advances in this technology provide high-throughput flow rates and the detection of relatively rare events in dilute admixed samples, enabling the application of flow cytometry to in vivo high-definition analyses of human cancers. The combination of flow sorting and genomic analyses has been recently used for the enrichment of pancreas carcinoma cells and to study the clonal composition of primary breast tumors. It was developed a methodology to adapt genomic DNA isolated from cytometrically purified nuclei for use with array comparative genomic hybridization (aCGH) and next-generation sequencing. The results produced high-definition genomic profiles of clonal populations from 40 pancreatic adenocarcinomas and a set of prostate adenocarcinomas, including serial biopsies from a patient who progressed to androgen-independent metastatic disease. The genomes of clonal populations were found to have patient-specific aberrations of clinical relevance. Furthermore, we identified genomic aberrations specific to therapeutically responsive and resistant clones arising during the evolution of androgen-independent metastatic prostate adenocarcinoma. It was also distinguished divergent clonal populations within single biopsies and mapped aberrations in multiple aneuploid populations arising in primary and metastatic pancreatic adenocarcinoma. It was proposed that our high-definition analyses of the genomes of distinct clonal populations of cancer cells in patients in vivo can help guide diagnoses and tailor approaches to personalized treatment. In summary, it was shown that flow cytometric-based separation followed by precise genomic characterization of sorted tumor (sub)populations provides a deep clonal analysis of the genomic heterogeneity present in human biopsies. It was proposed that this comprehensive clonal analysis of clinical samples provides insights into the evolution of each patient's tumor and their responses to therapeutic treatment and, in the era of personalized medicine, might also be considered for advancing effective therapeutic decisions [265].

Polymorphism

Although pancreatic cancer has been extensively studied, few risk factors have been identified, and no validated biomarkers or screening tools exist for early detection in asymptomatic individuals. We present a broad overview of molecular epidemiologic studies that have addressed the relationship between pancreatic cancer risk and genetic polymorphisms in several candidate genes and suggest avenues for future research. A comprehensive literature search was performed using the PubMed database. Overall, individual polymorphisms did not seem to confer great susceptibility to pancreatic cancer; however, interactions of polymorphisms in carcinogen-metabolizing genes, DNA repair genes, and folate-metabolizing genes with smoking, diet, and obesity were shown in some studies. The major problem with these studies is that, due to small sample sizes, they lack sufficient statistical power to explore gene-gene or gene-environment interactions. Another important challenge is that the measurement of environmental influence needs to be improved to better define gene-environment interaction. It is noteworthy that two recent genome-wide association studies of pancreatic cancer have reported that variants in ABO blood type and in 3 other chromosomal regions are associated with risk for this cancer, thus providing new insight into pancreatic cancer etiology. As is the case in other complex diseases, common, low-risk variants in different genes may act collectively to confer susceptibility to pancreatic cancer in individuals with repeated environmental exposures, such as smoking and red meat intake [266].

Breast cancer gene 1 and 2

Breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) gene mutations are most commonly linked with breast, ovarian, and prostate cancer. In pancreatic cancer, reports on the role of BRCA1 are inconsistent, whereas BRCA2 mutations are one of the initial mutations in PanIN progression of PDAC. BRCA2 plays a role in regulating the pathways involved in cell proliferation and differentiation. It shares a homology with c-Jun, acts as a transcriptional factor, is essential for cell division by cytokinesis, and participates with RAD51 in homologous repair of DNA double-strand breaks. Familial aggregation of pancreatic cancer with other cancers, such as breast cancers or melanomas, has been linked to the presence of BRCA2 mutations. BRCA2, FANCC, and FANCG gene mutations present in Fanconi syndrome caused predisposition of this subset to PDAC. In Ashkenazi Jews, mutations in BRCA1/2 are the major cause for pancreatic cancer. Cancer cells with BRCA2 gene alterations are sensitive to inhibitors of poly(ADP ribose) polymerase or DNA crosslinking agents (mitomycin C), both of which are more effective in the absence of intact homologous recombination repair systems. A patient with metastatic pancreatic cancer was found positive for BRCA2 mutations and responded really well to a third-line therapy with combination of mitomycin C and capecitabine. Some pancreatic cancers with mutated BRCA2 tend to change from being chemosensitive to DNA-intercalating agents to chemoresistant phenotypes. In such exceptional cases, mutated BRCA2 undergoes either a deletion of mutation or a secondary mutation, each of which would restore the wild type BRCA2 reading frame [251].

MicroRNAs

MicroRNAs are functional, 22nt, noncoding RNAs that negatively regulate gene expression. Recently, aberrant micro-RNA expressions have been implicated to have roles in the initiation and progression of certain diseases, including various cancers. A number of studies have demonstrated different roles of various types of miRNAs in the progression and survival of PC. A recent report claims that aberrant microRNA production is an early event in the development of PanIN. miRNAs exert their effect by regulating cell-cycle regulatory proteins. The expression of tumor protein 53-induced nuclear protein 1 (TP53INP1), which is

dramatically reduced in the early stages of pancreatic cancer, is repressed by the oncogenic microRNA miR-155, which itself was seen to be overexpressed in PDAC. Let-7 micro RNA, which targets K-ras oncogene, is present in normal acinar pancreatic cells but lost in poorly differentiated cancer samples. Among the target proteins regulated by miR-34 are Notch pathway proteins and Bcl-2, suggesting a role for miR-34 in the maintenance and survival of cancer stem cells. MicroRNA-21, which is significantly overexpressed in PC, has been extensively studied. Its strong expression predicts reduced survival in patients with node-negative disease and may be an important biologic marker for outcome. It contributes to cell proliferation, invasion, and chemoresistance of PC. Other sets of microRNAs found to be aberrantly expressed in pancreatic cancers are miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b, miR-15b, and miR-95,258, miR-155, miR-21, miR-221 and miR-222, miR-376a, and miR-301,259, miRNAs, miR-21, miR-210, miR-155, and miR- 196a,260, miR-155, miR-203, miR-210, and miR-222 [251].

MicroRNAs (miRNAs) are a class of posttranscriptional regulators that have recently introduced an additional level of intricacy to the understanding of gene regulation. There are currently over 10,000 miRNAs that have been identified in a range of species including metazoa, mycetozoa, viridiplantae, and viruses, of which 940, to date, are found in humans. It is estimated that more than 60 percent of human protein-coding genes harbor miRNA target sites in their 3' untranslated region and, thus, are potentially regulated by these molecules in health and disease. One review first briefly described the discovery, structure, and mode of function of miRNAs in mammalian cells, before elaborating on their roles and significance during development and pathogenesis in the various mammalian organs, while attempting to reconcile their functions with our existing knowledge of their targets. Finally, it was summarized some of the advances made in utilizing miRNAs in therapeutics [267].

MicroRNAs (miRNAs) have gained attention as an epigenetic component involved in the development of pancreatic ductal adenocarcinoma (PDAC). Several methods for miRNA profiling are in common use, but the validity of these methods is not defined. The aim of one study was to define the optimal method for miRNA detection in PDAC. miRNA expression was determined using different and partially redundant methods (miRNA microarray, TaqMan low density array (TLDA), single tube quantitative RT-PCR). The data from different methods were statistically evaluated and tested for intermethodic consistency and reliability of the results. Finally, the miRNA expression status and the cell lines' ability to metastasize were correlated. Comparing low and high metastatic cells, miRNA-microarrays identified fewer differentially expressed and only upregulated miRNAs (n=27; 27 up-regulated) compared with TLDA (n=54; 19 up- and 35 down-regulated). Evaluating miRNAs that target tumor suppressor genes, expression of all single tube quantitative real-time reverse transcriptase PCR (qRT-PCR) validated miRNAs was detected to be significantly altered in TLDA analysis (100 %). MiRNA microarrays detected only 25 percent of qRT-PCR validated miRNAs. Furthermore, results from TLDA analysis correlated well with data from qRT-PCR. Notable differences comparing data obtained from different screening methods were found. While TLDA and qRT-PCR correlated well in quantity and quality of the measured miRNAs, several tumor suppressor gene targeting and down-regulated miRNAs were not detected by miRNA-microarrays. This heterogeneity shows that care must be exercised when comparing results from different methods in PDAC [268].

p8

p8 is a stress gene whose activity is necessary for tumor development and progression. The acquisition of invasive properties by transformed cells is a key event in tumor development. In order to establish whether p8 is involved or not in this phenomenon, we assessed the capacity of p8 at influencing cell adhesion, migration, invasion, and tumorigenesis of pancreatic cancer cells. p8 expression was knocked down by a small interfering RNA

(siRNA) in pancreatic cancer-derived Panc-1 and MiaPaCa-2 cells and subsequent changes in cell adhesion, migration, invasion, and tumorigenesis were assessed. Influence of p8 silencing on gene expression was analyzed using cDNA microarrays. The influence of inhibiting CDC42, one of the genes most over-expressed in p8-silenced cells, on the changes observed in p8-silenced cells was also evaluated. Finally, the tumorigenic capacities of Panc-1 cells transfected with control siRNA or p8 siRNA were compared by assessing their ability to form colonies in soft agar and to grow as xenografts in nude mice. Knocking-down p8 in pancreatic cancer cells in vitro decreased migration and invasion while increasing cell adhesion; over-expression produced the opposite effect. Knocking down CDC42 reversed almost completely the effects of silencing p8 in vitro. Finally, cells transfected with p8 siRNA were almost unable to form colonies in soft agar. In addition, p8-deficient Panc-1 cells did not develop tumors when injected subcutaneously in nude mice. In conclusion, p8 expression controls pancreatic cancer cell migration, invasion and adhesion, three processes required for metastasis, at least in part, through CDC42, a major regulator of cytoskeleton organization [269].

p16INK4A

The CDKN2A locus on chromosome 9q21 encodes two tumor suppressor genes, p16INK4A and p14ARF. The p16INK4A gene regulates cell-cycle progression by inhibiting cyclin D/CDK4/6 complexes, which in turn inhibit of Rb phosphorylation. The interaction of p14ARF with mdm2 leads to p53 activation. In pancreatic-cancer development, inactivation of p16INK4A seems to be of greater importance than inactivation of p14ARF because germline and sporadic mutations have been identified that target p16INK4A and leave p14ARF intact. Germline mutations in p16INK4A are associated with the familial atypical mole malignant melanoma syndrome, which is characterized by a high incidence of melanoma, as well as a 13-fold increased risk of pancreatic cancer. The appearance and age of onset of pancreatic adenocarcinoma are variable among familial atypical mole malignant melanoma kindred with p16INK4A mutations, indicating a modulating role for environmental factors in disease penetrance. In sporadic PDAC, loss of p16INK4A function by mutation, deletion, or promoter hypermethylation occurs in 80 to 95 percent cases of PDAC. p16INK4A loss occurs at one of the earlier stages of PanIN and is generally seen in moderately advanced lesions that show features of dysplasia. p16INK4A alterations were also observed in a considerable number of PanIN1 in chronic pancreatitis tissues not associated with pancreatic cancer. Therefore, p16INK4A alterations, especially promoter methylation, might indicate high-risk precursors in chronic pancreatitis that might progress to cancer. p16INK4A methylation may also be a useful indicator of the potential malignancy of pancreatic epithelial cells. p16INK4A alterations were shown to have a bearing on the aggressiveness of PDAC, either alone or in combination with other polymorphisms in other genes such as K-ras, cyclin D1, Smad4, and p53 [251].

p21 (CIP1)

p21(CIP1) is a cyclin-dependent kinase inhibitor, which binds to and inhibits the activity of cyclin A, cyclin E, cyclin D1, and CDK2 and thus functions as a regulator of cell-cycle progression at G1. It can also inhibit phosphorylation of retinoblastoma through these complexes. By regulating the expression of p21 through p53, cells mediate the p53-dependent cell cycle G1 phase arrest in response to a variety of stress stimuli. And by inhibiting p21 (CIP1) expression, Myc favors the initiation of apoptosis, thereby influencing the outcome of a p53 response in favor of cell death. Mutated p21 alone and particularly in the presence of p27 mutations contributes to susceptibility to pancreatic cancer. Patients with altered p21 have a poor prognosis. Median survival among patients with resected pancreatic cancer who received adjuvant chemoradiation with p21(WAF1)-positive tumors was significantly longer than in patients with no p21(WAF1) staining (25 vs 11 months). The authors therefore proposed that alternate strategies for adjuvant therapy should be explored

for patients with pancreatic cancer who lack functional p21 (WAF1) [251].

p27

p27 binds to and prevents the activation of cyclin EYCDK2 or cyclin DYCDK4 complexes and thus controls the cell-cycle progression at G1. The degradation of this protein, which is triggered by its CDK-dependent phosphorylation and subsequent ubiquitination by SCF complexes, is required for the cellular transition from quiescent to the proliferative state. Mutation in p27, along with mutations in p21, can predict the susceptibility and early onset of pancreatic cancer. Some authors demonstrated a significant correlation of p27Kip1 mutations to prognosis, whereas others could not. The reason for such discordance in observations could be due to its significant correlation to only stage I and II disease. Loss of expression of p27 significantly correlates with some clinicopathologic variables such as lymph node metastasis, tumor grade, and clinical stage, implicating its role in metastasis and progression of the disease. Interestingly, in pancreatic neuroendocrine tumors, the retention of p27 expression associates with more metastatic disease. Mutations in a few novel molecules, some of which are human G-gamma, JAB1, MMP-9, and KLF4, influence pancreatic cancer progression and outcome in a p27-dependent manner [251].

Insensitivity to growth-inhibitory signals is an important step in carcinogenesis. Antigrowth signals ultimately exert their effects by controlling the cell cycle. The p27 tumour suppressor gene is a cyclin-dependent kinase (CDK) inhibitor that negatively regulates G1–S transition by binding and inactivating Cdk2/cyclin E and Cdk2/cyclin A complexes. Deregulation of cyclin and CDK activity may result in failure to induce cell cycle arrest, resulting in uncontrolled proliferation and accumulation of malignant cells. Expression of p27 has been shown to be an independent prognostic factor in a variety of human malignancies, including breast, colonic and prostate cancers. Studies of p27 expression have also suggested a prognostic effect on pancreatic cancer survival. In three studies p27 expression was an independent prognostic factor for improved survival, although the effect was limited to stage I and II disease in one of the studies. Reported rates of p27 positivity in tumour specimens vary from 30 to 50 percent. Other studies found that p27 added no prognostic information. The impact of p27 expression on pancreatic cancer prognosis remains inconclusive [248].

p53

The *p53* tumour suppressor gene is a negative regulator of the cell cycle at the G1/S and G2/M interfaces. p53 is also involved in DNA repair and the control of apoptosis. Mutation of this gene is the most frequent genetic alteration found in human cancer. Approximately 50-70 percent of pancreatic adenocarcinomas have inactivating p53 mutations, with positive IHC staining. The role of *p53* mutations in pancreatic carcinogenesis is well established, but it remains uncertain whether the presence of p53 overexpression has any prognostic implications. Two IHC studies demonstrated that patients with p53-positive tumours had a poorer outcome, although the effect was limited to advanced-stage disease in one of the studies. Several studies have found no correlation between p53 and survival [248].

p53 is a stress-inducible transcription factor that exerts this protective effect through the induction of either cell cycle arrest or programmed cell death (apoptosis) in damaged or stressed cells. The decision between the alternative end points of p53 activation mainly depends on Myc, but other mediators, cofactors, or posttranslational modifications of p53 itself (phosphorylation, acetylation, etc) may also play a role. In normal, unstressed conditions, p53 protein levels are kept very low by its negative regulator mdm2, which catalyzes the conjugation of ubiquitin molecules to p53. Because p53 itself is a positive regulator of mdm2, in tumors with mutated p53, high levels of inactive p53 accumulate. Under cellular stress, p53 protein is modified in a variety of ways (e.g. phosphorylation, acetylation) that allows it to evade mdm2-mediated degradation. The resulting increase in

steady-state levels of p53 and a possible increase in its affinity for DNA lead to the induction of transcription of genes that lead to cell cycle arrest or apoptosis. In tumors, this function of p53 is lost, resulting in cell survival and progression through the cell cycle, even after serious cellular insult that may have caused genomic damage. p53 is somatically mutated in 50 to 75 percent of the PDAC cases. Depending on their impact on structure and function, p53 mutations fall into 2 general classes:

- DNA contact mutations, which change the residues directly involved in contact with DNA but have modest impact on p53 conformation
- structural mutations that dramatically alter the conformation of p53. Among all p53 mutations, there are 4 hotspot mutations at residues 175, 248, 249, and 273.66

Although a few authors have shown a significant correlation of p53 expression with patient survival, for the most part it is conflicting. The reason for such conflicting results may be that the absence of p53 expression is not always synonymous with normal function of the p53 gene. On the one hand, p53 inactivation may render tumor cells more sensitive to certain anticancer agents, such as cisplatin, because of loss of the ability to repair drug-induced DNA damage; on the other hand, there may be a gain in function by the mutant p53, making it acquire new oncogenic activities to promote cancer by an increase in resistance to chemotherapy (e.g. 5-fluorouracil) and apoptosis. Gain of function may be because of the retention of protein-protein interaction with cellular proteins by mutant p53. Mutated p53 has been shown to interact with p73, Id2 (inhibitor of differentiation), and hnRNPK and suppress their functions, resulting an increase in the proliferative potential of the disease. Gene therapy based on restoration of wild type p53 protein function in pancreatic tumor cells with high amount of mutant p53 can be a feasible option in PDAC treatment [251].

Microarrays

The global gene expression analysis of cancer and healthy tissues typically results in large numbers of genes that are significantly altered in cancer. Such data, however, has been difficult to interpret due to the high level of variation of gene lists across laboratories and the small sample sizes used in individual studies. In one investigation, it was compiled microarray data obtained from the same platform family from 84 laboratories, resulting in a database containing 1,043 healthy tissue samples and 4,900 cancer samples for 13 different tissue types. The primary cancers considered included adrenal gland, brain, breast, cervix, colon, kidney, liver, lung, ovary, pancreas, prostate and skin tissues. It was normalized the data together and analyzed subsets for the discovery of genes involved in normal to cancer transformation. The integrated significance analysis of microarrays approach produced top 400 gene lists for each of the 13 cancer types. These lists were highly statistically enriched with genes already associated with cancer in research publications excluding microarray studies. The genes MTIM and RRM2 appeared in nine and TOP2A in eight lists of significantly altered genes in cancer. In total, there were 132 genes present in at least four gene lists, 11 of which were not previously associated with cancer. The list contains 17 metal ions and 15 adenylyl ribonucleotide binding proteins, six kinases and six transcription factors. The results point to the value of integrating microarray data in the study of combination drug therapies targeting metastasis [270].

Germ-line genetic variation may affect clinical outcomes of cancer patients. It was applied a candidate-gene approach to evaluate the effect of putative markers on survival of patients with pancreatic cancer. It was also examined gene-radiotherapy and gene-chemotherapy interactions, aiming to explain interindividual differences in treatment outcomes. In total, 211 patients with pancreatic cancer were recruited in a population-based study. Sixty-four candidate genes associated with cancer survival or treatment response were selected from existing publications. Genotype information was obtained from a previous genome-wide

association study data set. The main effects of genetic variation and gene-specific treatment interactions on overall survival were examined by proportional hazards regression models. Fourteen genes showed evidence of association with pancreatic cancer survival. Among these, rs1760217, located at the DPYD gene; rs17091162 at SERPINA3; and rs2231164 at ABCG2 had the lowest P of 10^{-4.60}, 0.0013, and 0.0023, respectively. It was also observed that two genes, RRM1 and IQGAP2, had significant interactions with radiotherapy in association with survival, and 2 others, TYMS and MET, showed evidence of interaction with 5-fluorouracil and erlotinib, respectively. The study thus suggested significant associations between germ-line genetic polymorphisms and overall survival in pancreatic cancer, as well as survival interactions between various genes and radiotherapy and chemotherapy [271].

Biomarkers for pancreatic cancer

By the time patients are diagnosed with pancreatic cancer, circulating cancer cells probably exist. Therefore, the detection of pancreatic cancer cells in the peripheral circulation could be used to diagnose early pancreatic cancer, which would otherwise not be detected by current imaging methods. The expression levels of h-TERT, CK20, CEA, and C-MET were detected in a model of circulating micrometastasis in pancreatic cancer that were enriched using immuno-magnetic separation of the circulating cancer cells. The sensitivity and specificity of the measurements were evaluated. The expression of the above genes was measured in the circulating cancer cells of pancreatic cancer patients. It was compared their expression rate in pancreatic cancer patients at different stages to screen for the indicator with highest sensitivity and specificity for the detection of circulating pancreatic cancer cells. Immuno-magnetic nanoparticles combined with RT-PCR enabled the detection of one tumor cell per 1×10⁷ peripheral blood mononuclear cells. The positive expression rates of C-MET, h-TERT, CK20, and CEA in the pancreatic cancer group were 80 percent (20/25), 100 percent (25/25), 84 percent (21/25), and 80 percent (20/25), respectively, while in the benign disease control group the rates were 0 percent (0/15), 0 percent (0/15), 7 percent (1/15), and 0 percent (0/15), respectively. There was a significant difference in the positive expression rate between the two groups. The specificity of h-TERT, CEA, and C-MET was higher than that of CK20. The positive expression rate of the four genes was not related to gender, age, tumor size, CA 19-9, or CEA serum levels. However, the positive expression of C-MET, CK20, and CEA closely correlated with tumor stage. Immuno-magnetic nanoparticles combined with RT-PCR were specific and sensitive for the detection of circulating cancer cells. It was concluded that the positive expression of C-MET, h-TERT, CK20, and CEA in the circulation of pancreatic patients could be used as an indicator for circulating cancer cells. The combined detection of the four genes improved the specificity and sensitivity to 100 percent, which may be attributable to the use of immuno-magnetic separation and enrichment of the circulating pancreatic cancer cells. The results suggest the clinical utility of this approach [272].

There is a need to identify prognostic subtypes of pancreatic ductal adenocarcinoma (PDAC) to predict clinical and therapeutic outcomes accurately, and define novel therapeutic targets. A large number of molecular tumour markers have been studied as potential prognostic markers. Unlike in breast and other carcinomas, no molecular markers have been established to date for estimating prognosis and adding information in treatment decision-making in patients with pancreatic cancer. Identification of biomarkers that accurately predict disease recurrence or response to chemotherapy would be of substantial aid in individual risk assessment and treatment selection, and may even lead to novel therapies by becoming targets for molecular intervention in specific subsets of patients. Immunohistochemical (IHC) analysis is used widely for evaluating molecular markers in clinical tissue specimens. Although several more sophisticated methods, such as cDNA microarray, fluorescence in situ hybridization and quantitative reverse transcriptase–polymerase chain reaction, are being translated into clinical practice, they are still impractical in routine clinical settings.

Relevant articles in English published between 1990 and 2010 were obtained from PubMed searches. Other articles identified from cross-checking references and additional sources were reviewed. The inclusion was limited to studies evaluating IHC markers in a multivariable setting. Database searches identified 76 independent prognostic and predictive molecular markers implicated in pancreatic tumour growth, apoptosis, angiogenesis, invasion and resistance to chemotherapy. Of these, 11 markers (Ki-67, p27, p53, transforming growth factor β 1, Bcl-2, survivin, vascular endothelial growth factor, cyclo-oxygenase 2, CD34, S100A4 and human equilibrative nucleoside transporter 1) provided independent prognostic or predictive information in two or more separate studies. Although some potential markers have been identified, a high degree of inconsistency between reports has been noted. Validation through large multicentre prospective studies using standardized protocols is still needed. Considering the complexity of the disease, it seems reasonable to hypothesize that panels of markers, rather than single proteins, might become useful. Because of clinical limitations, most studies have focused on predicting outcome after surgical resection. These patients account for only 20 percent of any pancreatic cancer cohort, and the present review cannot be assumed to be representative of the disease as a whole. None of the molecular markers described can be recommended for routine clinical use as they were identified in small cohorts and there were inconsistencies between studies. Their prognostic and predictive values need to be validated further in prospective multicentre studies in larger patient populations [248].

Pancreatic cancer has a high mortality rate since early diagnosis is difficult and radical operation is challenging. Classical tumor markers are reliable parameters to determine disease progression during chemotherapy or recurrence after surgery, but they are not adequate to identify suspected disease or for screening. Endoscopic brushing cytology or biopsy from the stenotic duct is widely performed for the histological evidence of pancreatic cancer, but still suffers from low sensitivity. Recently, several molecules were found to be specifically expressed in pancreatic cancer, and these novel molecular markers are reported to improve the sensitivity of cytology or biopsy. In some cases, novel markers are tested for the diagnosis of cystic neoplasms. In addition, advances in endoscopic ultrasonography-guided fine needle aspiration biopsy enabled sampling of the cancer tissue before surgery or treatment, which delineates the individualized therapeutic strategy against pancreatic cancer, via the assessment of prognosis- or therapy resistance-related factors. Furthermore, novel transcriptomic or metabolomic biomarkers in the clinical samples collected by non-invasive methods, e.g. blood or saliva samples, are now applied for the diagnosis of pancreatic cancer. These methods will be beneficial for the screening and early detection of pancreatic cancer [273].

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Protein profiles of endoscopically collected pancreatic juice from normal, chronic pancreatitis patients and pancreatic cancer patients were compared to identify diagnostic biomarkers of pancreatic cancer. Secretin was injected intravenously and pancreatic juice was collected via selective cannulation of the pancreatic duct during endoscopic retrograde cholangio-pancreatography. Pancreatic juices consisting of three pooled samples for normal control, chronic pancreatitis, and pancreatic cancer patients were compared using two-dimensional gel electrophoresis, and the proteins were subsequently identified using MALDI-TOF-MS. Thirty-five protein spots were up-regulated twofold in pancreatic cancer compared with the levels in the normal controls, and 85 protein spots were present in pancreatic cancer samples but not in normal controls. After excluding spots that were also expressed in chronic pancreatitis, 26 protein spots that were up-regulated or only expressed in pancreatic cancer samples were identified. Among the identified proteins, we confirmed the expressions of BIG2, PRDX6, and REG1 α in pancreatic cancer tissue using immunohistochemistry. ELISA showed that the serum level of REG1 α was significantly higher in patients with pancreatic cancer than it was in the normal controls. With the best cut-off value, the sensitivity and specificity of REG1 α to differentiate normal and pancreatic cancer were 83 and 82 percent, compared with 70 percent and 100 percent for CA19-9. It was shown that pancreatic juice is a good source of pancreatic cancer tumor markers. Further studies are needed to determine the clinical implications of REG1 α and other markers [275].

alpha-Fetoprotein

It was aimed to demonstrate the existence of cancer stem cells in human pancreatic cancer, and to clarify that they are alpha-fetoprotein (AFP) producing cells. Six cell lines derived from human pancreatic cancers were examined, and AsPC-1 and PANC-1 were noted to express AFP. Single cell culture assays and xenotransplantation revealed that the AFP-producing cells had the capacity for self-renewal and differentiation, and that these cells were tumorigenic. Furthermore, they were resistant to anti-cancer agents. The ABCA12 transporter was expressed in the AFP-producing cells at a level more than twice as high as that in the non-AFP-producing cells. The AFP-producing cells were shown to be putative pancreatic cancer stem cells. Furthermore, the expression of ABCA12 appears to be associated with drug resistance [276].

Immunohistochemical prognostic markers

The potential prognostic value of several commonly investigated immunohistochemical markers in resected pancreatic cancer is variably reported. The objective of one study was to conduct a systematic review of literature evaluating p53, p16, smad4, bcl-2, bax, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) expression as prognostic factors in resected pancreatic adenocarcinoma and to conduct a subsequent meta-analysis to quantify the overall prognostic effect. Relevant literature was identified using Medline, EMBASE and ISI Web of Science. The primary end point was overall survival assessed on univariate analysis. Only studies analysing resected pancreatic adenocarcinoma were eligible for inclusion and the summary log^e hazard ratio (log_{HR}) and variance were pooled using an inverse variance approach. Hazard ratios greater than one reflected adverse survival associated with positive immunostaining. Vascular endothelial growth factor emerged as the most potentially informative prognostic marker (11 eligible studies, n=767, HR=1.51 (95 % confidence interval 1.18 to 1.92)) with no evidence of any significant publication bias. Bcl-2 (5 eligible studies, n=314, HR=0.51 (95% CI=0.38-0.68)), bax (5 studies, n=274, HR=0.63) and p16 (3 studies, n=229, HR=0.63) also returned significant overall survival differences, but in smaller patient series due to a lack of evaluable literature. Neither p53 (17 studies, n=925, HR=1.22), Smad4 (5 studies, n=540, HR=0.88) nor EGFR (4 studies, n=250, HR=1.35) was found to represent significant prognostic factors when analysing the pooled patient data. There was evidence of significant heterogeneity in four of the seven study groups. These results support the case for immunohistochemical expression

of VEGF representing a significant and reproducible marker of adverse prognosis in resected pancreatic cancer [277].

Mast cells

Recently, there is evidence that the number of mast cells in various solid cancers increases with tumor progression. The role of mast cells in promoting tumor progression, however, has not been well studied in pancreatic ductal adenocarcinoma (PDAC). The aim of one study was to investigate the prognostic value of mast cell counts in different zones of the neoplasm in patients with PDAC after curative resection. Numbers of mast cells and microvessels were assessed by immunohistochemistry in tissues from 103 patients with PDAC and 10 patients with normal pancreas. All patients with PDAC underwent partial pancreatic resection. The investigators paid particular attention to the distribution of mast cells in each specimen. High mast cell counts in the intratumoral border zone correlated with the presence of lymphatic and microvascular invasion, lymph node metastasis, and TNM stage, and were an independent prognostic factor for overall survival. In contrast, neither in the intratumoral center zone nor in the peritumoral zones was mast cell count associated with OS. Mast cell counts in the intratumoral border zone, but not in the peritumoral or in the intratumoral center zone, were correlated with microvessel counts. The study shows a zone-specific distribution of mast cells in PDAC and highlights the importance of invasive front in the prognosis of patients with PDAC after curative resection. Zone-specific evaluation of mast cell and microvessel counts may be helpful for prognostic assessment and therapeutic decision making in PDAC [278].

Conventionell tumor markers

CA 19-9

Although highly sensitive and/or specific biomarkers for pancreatic cancer are lacking, CA 19-9 levels are frequently used to help determine resectability or as an indicator of treatment response. One report demonstrates that CA 19-9 may also be a valuable predictive or prognostic variable. CA 19-9 levels, total bilirubin, pathologic findings, and survival were evaluated among 143 patients who underwent pancreatoduodenectomy between 2001 and 2006 at the Mayo Clinic, and CA 19-9 levels were associated with increased overall and recurrence-free survival. Researchers used Cox proportional hazards model to determine a cutoff value for CA 19-9 of 120 U/mL, and observed overall survival at 1, 3, and 5 months for patients with subthreshold CA 19-9 to be 76, 41, and 31 percent, respectively, while it was 64, 17, and 10 percent, respectively, for patients with a preoperative serum CA 19-9 level greater than 120 U/mL, which was a significant difference. Higher CA 19-9 levels were not associated with a greater chance of an R1 or R2 resection, tumor involving the margin of the superior mesenteric artery or at the portal vein groove, or lymph node metastases [203].

Staging of pancreatic cancer

Clinical staging

Local or resectable (about 10 %, median survival 17–23 months)

- Stage 0 (Tis, N0, M0)
- Stage IA (T1, N0, M0)
- Stage IB (T2, N0, M0)
- Stage IIA (T3, N0, M0)
- Stage IIB (T1, N1, M0; T2, N1, M0; T3, N1, M0)

Borderline resectable (10 %, median survival up to 20 months) Stage 3 disease with tumour abutment or $<180^\circ$ circumference of the superior mesenteric artery or celiac arteries, or a short segment of hepatic artery or the superior mesenteric vein, pulmonary vein, or confluence of these veins. Locally advanced or unresectable (about 30 %, median survival 8-14 months)

- Stage III (T4, any N, M0)

Tumour encasement $>180^\circ$ circumference of the superior mesenteric artery or coeliac arteries, any unreconstructable venous involvement. Metastatic (about 60 %, median survival 4-6 months)

- Stage IV (any T, any N, M1)

TNM classification

T=primary tumour

TX: primary tumour cannot be assessed

T0: no evidence of primary tumour

Tis: carcinoma in situ (includes the PanIN 3 classification)

T1: tumour restricted to the pancreas, ≤ 2 cm greatest dimension

T2: tumour restricted to the pancreas, >2 cm greatest dimension

T3: tumour extends beyond the pancreas, no involvement of coeliac axis or superior mesenteric artery (or extension to the portal vein or superior mesenteric artery, but still resectable)

T4: tumour affects the coeliac axis or superior mesenteric artery (unresectable primary tumour)

N=regional lymph node

NX: regional lymph nodes cannot be assessed

N0: no regional lymph-node metastasis

N1: regional lymph-node metastasis

M=distant metastasis

M0: no distant metastasis

M1: distant metastasis

Timing for staging

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a propensity for early metastasis that is often encountered unexpectedly at operation. The objective was to examine the effect of the time interval between preoperative imaging and attempted resection and the venue in which imaging was performed on the frequency of unanticipated metastasis (UM) encountered at operation. It was hypothesized that imaging obtained locally at the hospital where surgery should be done and within 4 weeks of operation will result in a lesser frequency of UM encountered at operation. Between 2004 and 2009, records of patients undergoing planned pancreatic resection for PDAC at a high volume pancreatic surgery center were compiled. Exclusion criteria included neoadjuvant therapy, prior pancreatic resection, or evidence of metastasis on imaging. Review and analysis of clinical, radiographic, operative, and pathologic data were undertaken. Frequency of UM and outcome of resection was compared with the interval between most recent cross-sectional imaging (dual-phase contrast-enhanced CT or MRI) and operation defined as imaging-to-operation interval (IOI). Four-hundred eighty-seven patients met eligibility requirements for the study: 431 (88 %) proximal and 56 (12 %) distal PDAC. 202 (41 %) patients had their most recent imaging performed at an outside institution, and no difference in the rates of UM was observed whether imaging was conducted at our institution or at an outside institution. Of 329 with complete imaging information for analysis, UM were discovered in 60 (18 %): 52 (18 %) of 293 proximal PDAC and 8 (22 %) of 36 distal PDAC. In proximal PDAC, there was a linear relationship in the frequency of UM as a function of the weekly IOI. For distal PDAC,

no significant difference in the frequency of UM as a function of IOI was observed. For proximally located PDAC, the frequency of UM increases with greater imaging-to-operation interval. Performing imaging at a high volume, pancreatic surgery center compared with elsewhere was not associated with a decrease in the rate of UM. Obtaining timely diagnostic imaging for proximal PDAC may improve the accuracy of preoperative staging, and thereby reduce the number of operations not producing oncologic benefit [279].

Pancreas-protocol imaging at staging of pancreatic adenocarcinoma

High-quality preoperative cross-sectional imaging is vital to accurately stage patients with pancreatic ductal adenocarcinoma (PDAC). It was hypothesized that imaging performed at a high-volume pancreatic cancer center with pancreatic imaging protocols more accurately stages patients compared with pre-referral imaging. It was retrospectively reviewed data from all patients with PDAC who presented to a surgical oncology clinic between 2005 and 2009. Detailed preoperative imaging, staging, and operative data were collected for each patient. A total of 230 patients with PDAC were identified, of which 169 had pre-referral imaging. Patients were selectively reimaged at our institution based on the quality and timing of imaging at the outside facility: 108 (47 %) patients were deemed resectable, 54 (24 %) were deemed borderline-resectable, and 68 (30 %) were deemed unresectable. Of the resectable patients, 99 opted for resection. Eighty-two of those 99 patients underwent preoperative imaging at our institution, and of these 27 percent had unresectable disease at the time of surgery compared with 47 percent of patients who only had pre-referral imaging. Reimaging altered staging and changed management in 56% of patients. Among that group were 55 patients, categorized as resectable on pre-referral imaging, who on repeat imaging were deemed to be borderline resectable (n=27) or unresectable (n=28). Pancreas-protocol imaging at a high-volume center improves preoperative staging and alters management in a significant proportion of patients with PDAC who undergo pre-referral imaging. Thus, repeat imaging with pancreas protocols and dedicated radiologists is justified at high-volume centers [280].

Histopathological pathophysiology

Pancreatic ductal adenocarcinomas evolve through noninvasive precursor lesions, most typically pancreatic intraepithelial neoplasias acquiring clonally selected genetic and epigenetic alterations along the way. Pancreatic cancers can also evolve from intraductal papillary mucinous neoplasms and mucinous cystic neoplasms. Non-invasive precursors to pancreatic cancer [213]:

- the most common neoplastic precursor to invasive adenocarcinoma of the pancreas is known as PanIN
- PanINs are microscopic (<5 mm diameter) and are not directly visible by pancreatic imaging
- PanINs can harbour the somatic genetic alterations seen in invasive pancreatic cancers, and prevalence of these genetic alterations rises as the amount of cytological and architectural atypia in PanINs increases
- Low-grade PanINs (PanIN 1) are very common with increasing age and high-grade PanINs (PanIN 3) are usually present in pancreata with invasive cancer
- Pancreata resected from individuals with a strong family history of pancreatic cancer usually have multifocal PanINs associated with lobulocentric atrophy
- Molecular markers are being investigated to see if they can be used to estimate the burden and grade of PanIN
- Molecular imaging has the potential to detect PanIN

- Intraductal papillary mucinous neoplasms are a less frequent precursor to invasive pancreatic cancer; they are large cystic neoplasms (≥ 5 mm) diagnosed increasingly because of improvements in pancreatic imaging
- Non-invasive intraductal papillary mucinous neoplasms are classified on the basis of the amount of cytological and architectural dysplasia, as either low-grade, intermediate-grade, or high-grade dysplasia (carcinoma in situ)
- Cure rates are very high after resection of intraductal papillary mucinous neoplasms that do not have an associated invasive pancreatic cancer but, if left alone, these lesions can progress to incurable invasive cancers

Precursor lesions

Early onset pancreatic cancer (EOPC) constitutes less than 5% of all newly diagnosed cases of pancreatic cancer (PC). In one study, it was aimed to describe histopathological picture of extratumoral parenchyma in 23 cases of EOPCs (definition based on the threshold value of 45 years of age) with particular emphasis on two types of precursor lesions of PC: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs). The types, grades, and densities of precursor lesions of PC were compared in patients with EOPCs, in young patients with neuroendocrine neoplasms (NENs), and in older (at the age of 46 or more) patients with PC. The study included 23 out of 26 EOPC cases, 13 out of 22 NEN cases in young patients (the two additional enucleated tumors not taken into account), and 41 out of 44 PCs in older patients. Among 23 studied patients with EOPCs (main study group), PanINs were found in 22 (96 %) of them. PanINs-3 were found in nine (39 %) cases. The overall PanIN density ranged from 0.0 to 2.00 lesions per cm^2 of EPP. The PanIN-3 density ranged from 0.0 to 0.60 lesions per cm^2 of EPP. IPMNs or incipient IPMNs were not found in any other EOPC cases. FLAs were present in 13 cases (from one to five lesions per case); in seven of them, they showed features of mucinous tubular complexes. The FLA to PanIN rate ranged from 0.0 to 0.66, whereas the rate of mucinous tubular complexes to PanINs ranged from 0.0 to 0.33. Two patients showed features of moderate to marked chronic obstructive pancreatitis. Densities of PanINs of all grades were significantly larger in EPP of patients with EOPCs as compared to EPP of young patients with NENs. However, there were no differences concerning the rate of FLAs to PanINs and the rate of mucinous tubular complexes to PanINs between those groups of patients. IPMN was found only in a single patient with EOPC but in 20 percent of older patients with PC. PanINs are the most prevalent precursor lesions of EOPC. IPMNs are rarely precursor lesions of EOPC. Relatively high density of low-grade PanINs-1 in extratumoral parenchyma of patients with EOPC may result from unknown multifocal genetic alterations in pancreatic tissue in patients with EOPCs [281].

Pancreatic intraepithelial neoplasia (PanIN) is a well-recognized and extensively studied precursor lesion of pancreatic cancer of ductal lineage. PanINs may present as flat, micropapillary, or papillary noninvasive intraductal lesions, which usually develop within small pancreatic ducts (less than 5 mm or less than 10 mm in diameter). PanINs are divided into four categories based on grade of dysplasia (1A, 1B, 2, and 3). Low-grade PanINs (PanINs-1A, PanINs-1B, PanINs-2) may be found in pancreata of 16-80 percent of individuals without any clinically detectable pancreatic disease. In contrast, PanINs-3 are very rarely seen in pancreata of individuals without pancreatic cancer. In a proportion of cases, PanINs (particularly low grade ones) may be associated with obstruction of branch pancreatic ducts. This may lead to localized atrophy of pancreatic lobule (focal lobular atrophy, FLA) drained by the affected duct and subsequent focal fibrosis of the pancreatic parenchyma. Atrophy and fibrosis within areas of FLA are frequently associated with acinar-ductal metaplasia and formation of so-called tubular complexes. Tubular complexes may develop within atrophic lobules with or without associated PanIN within a draining duct. At the advanced stage of this process, mucinous metaplasia within ductules of tubular complexes may develop (mucinous tubular complexes). It should be distinguished from PanIN (i.e. mucinous change within pre-

existing duct). PanINs and FLAs are more frequent in older individuals, and therefore, they are believed to represent an age-related phenomenon. However, PanIN-FLA complexes are particularly frequent in pancreata of individuals with a strong family history of PC. This may be very useful for screening of persons with high risk of developing PC, since FLAs may be visualized by endoscopic ultrasonography [281].

PanINs are very frequent in adult pancreata (up to 80 % of cases studied), but the prevalence rates of PanIN of different grades of dysplasia differ significantly. PanINs-1A lesions are more prevalent (19-68 %) as compared to PanINs-1B (12-20 %) and PanINs-2 lesions (0-14 %). Concerning the issue of PanIN prevalence in individuals without detectable pancreatic diseases, PanINs are more prevalent in older persons in comparison to younger ones. However, it is not definitely clear if the grade of PanINs found in asymptomatic individuals increases with their age, since results of different studies are discrepant. Even if such a correlation exists, it is rather weak. There is no significant difference between genders in the prevalence of PanINs. The PanIN prevalence is not associated with history of tobacco smoking or alcohol abuse. Is it not definitely clear whether PanIN prevalence is higher in the pancreatic head in comparison to other segments. It is clear that PanIN-2 and PanIN-3 lesions are not supposed to be found in young patients without PCs, but they exist in patients with PCs (both younger and older ones) [281].

Taken together it is clear that PanINs is the most prevalent precursor lesion of EOPCs. PanINs of all grades are frequent but not the universal finding in EPP in patients with EOPCs. The density of all grades of PanINs in EPP is significantly higher in patients with EOPCs than in young patients with NENs. Density of PanINs-1A is higher in patients with EOPCs than in older patients with PCs, but densities of PanINs of other grades are comparable. Some of PanINs are related to FLAs with or without formation of mucinous tubular complexes. EOPCs less frequently than PCs in older patients are derived from IPMNs. Relatively high density of low-grade PanINs in EPP of patients with EOPCs as compared to young patients with NENs and older patients with PCs may result from unknown multifocal genetic alterations in pancreatic tissue of EOPC patients [281].

Screening to detect curable precursor lesions

Screening high-risk individuals with imaging tests, such as endoscopic ultrasound and computed tomography, can lead to the detection and treatment of predominantly asymptomatic premalignant lesions. These pancreatic lesions consist of resectable, mostly branch-type non-invasive intraductal papillary mucinous neoplasms. Endoscopic ultrasound features of chronic pancreatitis are highly prevalent in high-risk individuals and these directly correlate with multifocal lobulocentric parenchymal atrophy due to pancreatic intraepithelial neoplasia. Long-term, multi-prospective studies are needed to determine if screening for early pancreatic adenocarcinoma and timely intervention will result in decreased pancreatic cancer incidence and mortality in high-risk individuals [282].

There have been efforts to screen individuals with an inherited predisposition for early curable disease – such as pancreatic intraepithelial neoplasias, and noninvasive intraductal papillary mucinous neoplasms and mucinous cystic neoplasms. Family history has been used as a quantitative predictor of pancreatic cancer risk. Indeed, screening has identified silent pancreatic neoplasia in many individuals with strong family histories of pancreatic cancer. However, screening brings with it the risk of over-treatment, and the randomised trials needed to ascertain if pancreatic cancer screening can save lives have not been undertaken. Researchers are doing clinical trials to assess the best screening protocol for individuals at increased risk of pancreatic neoplasia. An ideal screening test for early pancreatic cancer would be a highly accurate blood marker that could be measured fairly non-invasively. Unfortunately, none to date have proven sufficiently specific for diagnosis.

Furthermore, the focus of screening efforts up to now has been to detect preinvasive lesions, rather than early pancreatic cancer, since resection of preinvasive lesions can prevent development of an invasive pancreatic cancer, whereas once an invasive pancreatic cancer develops, its spread beyond the pancreas is probably rapid, restricting use of markers of invasive pancreatic cancer. Because of its ability to detect small preinvasive lesions (of about 1 cm), endoscopic ultrasound is used widely as a screening test. Since microscopic pancreatic intraepithelial neoplasias are usually not visible by pancreatic imaging, research is attempting to identify markers in pancreatic fluid that could reliably identify high-grade pancreatic intraepithelial neoplasias. Focal preinvasive lesions evident by endoscopic ultrasound (such as intraductal papillary mucinous neoplasms) are probably most readily sampled with fine-needle aspiration [213].

Pancreatic cancer surveillance and screening

Several risk factors have been reported regarding the development of pancreatic cancer. These risk factors include family history, accompanying diseases, and lifestyle/personal habits. Family history includes that of pancreatic cancer and hereditary pancreatic cancer syndrome. Accompanying diseases that increase the risk include diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatic cancer syndrome and intraductal papillary mucinous neoplasms. Lifestyle-associated factors include smoking and diet. Detailed examination of patients with such risk factors is warranted, but the cost-benefit effect should be considered. Thus, patients with more than one risk factor should be carefully followed up, and periodic examination of such patients is necessary to ensure the detection of smaller and less-advanced pancreatic cancer lesions and thus to improve the clinical outcome of patients with pancreatic cancer [283].

The concept of pancreatic cancer prevention through surveillance of high-risk patients has come of age. It is cost-effective to provide surveillance of patients who have a lifetime risk of pancreatic cancer that is ≥ 16 percent. Studies are currently ongoing that contribute to the understanding of the imaging methodologies that are best suited for surveillance and the best algorithm for the clinical management of patients who are at risk of this highly lethal disease. Long-term outcomes analyses will help shed light on the best management of these patients, as well as a better understanding of the natural history of familial pancreatic cancer [284].

Strategies to improve disease-specific outcome of pancreatic cancer include identification and early detection of precursor lesions or early cancers in high-risk groups. In one study, it was investigated whether screening at-risk relatives of familial pancreatic cancer (FPC) patients is safe and has significant yield. It was enrolled 309 asymptomatic at-risk relatives into our Familial Pancreatic Tumor Registry (FPTR) and offered them screening with magnetic resonance cholangiopancreatogram (MRCP) followed by endoscopic ultrasound (EUS) with fine needle aspiration if indicated. Relatives with findings were referred for surgical evaluation. So far 109 relatives had completed at least one cycle of screening. Abnormal radiographic findings were present on initial screening in 18/109 patients (17 %), 15 of whom underwent EUS. A significant abnormality was confirmed in 9 of 15 patients, 6 of whom ultimately had surgery for an overall diagnostic yield of 8 percent (9/109). Yield was greatest in relatives >65 years old (35 %, 6/17) when compared with relatives 55-65 years (3 %, 1/31) and relatives <55 years (3 %, 2/61). It was concluded that screening at-risk relatives from FPC families has a significant diagnostic yield, particularly in relatives >65 years of age, confirming prior studies. MRCP as initial screening modality is safe and effective [285].

Symptoms and signs

Jaundice is a yellowish pigmentation of skin and mucous membranes caused by hyperbilirubinemia, which itself has various causes. Jaundice related to malignant tumors is classified as obstructive jaundice. This disease proceeds from biliary tract obstruction and liver failure by progression of intrahepatic tumors, including metastases from other malignancies. Biliary tract cancer, pancreatic head cancer, or lymph nodes metastases from other sites of cancer are mainly responsible for the obstruction of the bile duct. In patients with obstructive jaundice, biliary drainage is often required in order to give treatments such as chemotherapy. In patients with biliary drainage, various complications arise, such as cholangitis due to obstruction of a biliary stent, and bleeding from the ulcer due to a dislodged stent to the duodenum. It is crucial to manage those complications as oncologic emergencies. Jaundice of liver failure due to hepatic metastases is often observed in patients with gastrointestinal malignancies such as gastric cancer or colorectal cancer. Although chemotherapy is the usual application for those patients, useful anti-cancer agents are limited. It is crucial to diagnose and decide the best treatments as soon as possible for patients with very advanced hepatic metastases [286].

Early-stage pancreatic cancer is usually clinically silent, and disease only becomes apparent after the tumour invades surrounding tissues or metastasises to distant organs. Pancreatic cancer patients who have undergone abdominal CT scans for other reasons before their diagnosis are usually noted in retrospect to have had subtle abnormalities suspicious for pancreatic cancer up to 1 year before development of symptoms, suggesting a missed opportunity for early detection. Typical presenting symptoms of pancreatic cancer include abdominal or mid-back pain, obstructive jaundice, and weight loss. Weight loss can arise from anorexia, maldigestion from pancreatic ductal obstruction, and cachexia. Occasionally, pancreatic-duct obstruction could result in attacks of pancreatitis. Deep and superficial venous thrombosis is not unusual and might be a presenting sign of malignant disease. Gastric-outlet obstruction with nausea and vomiting sometimes happens with more advanced disease. Less common manifestations include panniculitis and depression. About 25 percent of patients with pancreatic cancer have diabetes mellitus at diagnosis and roughly another 40 percent have impaired glucose tolerance. The cause of the diabetogenic state is uncertain, but diabetes is sometimes cured by resection of pancreatic cancer. Most people with new-onset diabetes, however, do not have pancreatic cancer. Apart from weight loss, few clinical clues exist to suspect pancreatic cancer in those with new-onset diabetes [213].

Diagnostics

The purpose of one study was to assess whether habitus and organ enhancement influence iodine subtraction and should be incorporated into spectral subtraction algorithms. The study included 171 patients. In the unenhanced phase, MDCT was performed with single-energy acquisition (120 kVp, 250 mAs) and in the parenchymal phase with dual-energy acquisitions (80 kVp, 499 mAs; 140 kVp, 126 mAs). Habitus was determined by measuring trunk diameters and calculating circumference. Iodine subtraction was performed with input parameters individualized to muscle, fat, and blood ratio. Attenuation of the liver, pancreas, spleen, kidneys, and aorta was assessed in truly and virtually unenhanced image series. Pearson analysis was performed to correlate habitus with the input parameters. Analysis of truly unenhanced and virtually unenhanced images was performed with the Student t test; magnitude of variation was evaluated with Bland-Altman plots. Correction strategies were derived from organ-specific regression analysis of scatterplots of truly unenhanced and virtually unenhanced attenuation and implemented in a pixel-by-pixel approach. The correlations between habitus and blood ratio ($r = 0.694$) and attenuation variation of fat at 80 kVp ($r = -0.468$) and 140 kV ($r = -0.454$) were confirmed. Although overall mean attenuation

differed by no more than 10 HU between truly and virtually unenhanced scans overall, these differences varied by organ and were large in individual patients. Paired comparisons of truly and virtually unenhanced measurements differed significantly for liver, spleen, pancreas, kidneys, and aortic blood pool but paired comparisons of truly unenhanced and individually organ-corrected measurements did not differ when organ- and habitus-based correction strategies were applied. Habitus and organ enhancement influence virtually unenhanced imaging and should be incorporated into spectral subtraction algorithms [287].

Tri-phasic pancreatic-protocol CT is the best initial diagnostic test for pancreatic cancer. It is also best for disease staging, and optimum CT scans provide about 80 percent accuracy for prediction of resectability. The quality of CT varies, and imaging technology continues to improve. The ability of high-quality pancreatic-protocol CT scans to detect locally advanced and metastatic disease reliably has greatly reduced the number of unnecessary laparotomies and need for staging laparoscopies. Endoscopic ultrasound is also highly accurate for diagnosis of pancreatic cancer, and sampling for diagnostic cytology can be undertaken at the time of endoscopic ultrasound. MRI can be used for staging in patients who cannot tolerate intravenous contrast for CT. Chest imaging (either chest radiography or CT) is recommended to detect pulmonary metastases. PET CT is currently not part of routine staging but can be helpful if metastases are suspected, such as for indeterminate lesions by CT, and might be better at identification of metastatic disease. Laparoscopy can spot peritoneal metastases but is not undertaken routinely before proceeding with pancreatic resection. Preoperative amounts of CA19-9 of more than 100 or 200 U/mL predict unresectability. Cytological diagnosis can usually be made with endoscopic ultrasound or CT-guided fine-needle aspiration. Sensitivity of endoscopic ultrasound-guided fine-needle aspiration of pancreatic masses is reported to be about 80 percent. Identification of the cause of biliary or pancreatic-duct strictures might need ERCP and brushings for cytological diagnosis. The yield of cells from endoscopic brushings is low (about 20 %) because of the small sample and sometimes subtle differences between malignant and non-neoplastic reactive cells. Molecular markers could have a role as an adjunct to brush and fine-needle aspirate cytological diagnosis, but these need further evaluation. A biopsy specimen is not needed for surgical resection when suspicion of cancer is high; generally, the resection will provide therapeutic benefit, and substantially delaying surgery to confirm a diagnosis could set back commencement of effective treatment [213].

EUS

Endoscopic ultrasound (EUS) provides detailed, high-resolution images of the pancreas. However, whether a lesion is malignant or benign cannot be diagnosed solely from its imaging features on EUS. The introduction of EUS-guided fine needle aspiration (EUS-FNA) offers the possibility to obtain a cytological or histological diagnosis of pancreatic lesions with a high sensitivity and specificity. Although the clinical utility of EUS-FNA for pancreatic diseases is widely accepted, the indication for preoperative tissue diagnosis of pancreatic lesions suspected to be malignant is still controversial. One review highlighted the diagnostic potential of EUS-FNA, as well as its current indications and contraindications, complications, and techniques [288].

Contrast-enhanced ultrasonography

Since its introduction, contrast-enhanced ultrasonography (CEUS) has significantly extended the value of ultrasonography (US). CEUS can be used to more accurately determine pancreatic lesions compared to conventional US or to characterize lesions already detectable by US. Thus, CEUS can aid in the differential diagnosis of pancreatic tumors. Using US contrast media, it is possible to visually detect microvessels in the majority of pancreatic ductal adenocarcinomas. Thus, the use of quantitatively evaluated

transabdominal CEUS can help in the differentiation of patients with mass-forming pancreatitis from patients with pancreatic adenocarcinomas. In neuroendocrine pancreatic tumors, different enhancement patterns can be observed in relation to the tumor mass: larger ones show a rapid early enhancement sometimes combined with necrotic central structures, and smaller ones disclose a capillary-blush enhancement. Pseudocysts, the most widespread cystic lesions of the pancreas, are not vascularized. They do not show any signal in CEUS and remain entirely anechoic in all phases, while true cystic pancreatic tumors usually have vascularized septa and parietal nodules. In summary, CEUS is effective for differentiating solid pancreatic tumors in most cases. CEUS is safe and cost effective and can better discriminate solid from cystic pancreatic lesions, thereby directing further imaging modalities [289].

Endoscopic elastography

Sonoelastography is based on the knowledge that some diseases, such as cancer, lead to a change in tissue hardness. Elastography examines the elastic properties of tissues by applying a slight compression to the tissue and comparing the images obtained before and after this compression. Endoscopic ultrasonography (EUS) is today the best technique to diagnose a small pancreatic mass and to determine the histology of such lesions. However, the accuracy of EUS-FNA is around 85-90 percent. In one study, elastography was used to differentiate benign from malignant pancreatic masses. The bright future of the second generation of elastography, the quantitative elastography or ratio elastography, was also discussed [290].

CT

To assess positional reproducibility of pancreatic tumors under end-exhalation breath-hold conditions with a visual feedback technique based on computed tomography (CT) images. Ten patients with pancreatic cancer were enrolled in an institutional review board-approved trial. All patients were placed in a supine position on an individualized vacuum pillow with both arms raised. At the time of CT scan, they held their breath at end-exhalation with the aid of video goggles displaying their abdominal displacement. Each three-consecutive helical CT data set was acquired four times (sessions 1-4; session 1 corresponded to the time of CT simulation). The point of interest within or in proximity to a gross tumor volume was defined based on certain structural features. The positional variations in point of interest and margin size required to cover positional variations were assessed. It was shown that a margin size of 5 mm was needed to cover the 95th percentiles of the overall positional variations under end-exhalation breath-hold conditions, using this noninvasive approach to motion management for pancreatic tumors [291].

Computed tomography (CT) perfusion studies can provide valuable information regarding tumor vascularization. It was reported on a study assessing CT perfusion characteristics in the normal pancreas and in patients with pancreatic adenocarcinoma. Twenty healthy subjects and 20 patients with histologically confirmed pancreatic adenocarcinoma were included in the study. All subjects underwent perfusion CT imaging of the pancreas using 128-slice dual-source CT. The scanning sequence included 18 scans. Parametric maps of blood volume (BV), blood flow (BF), and permeability surface area product (PS) were generated and compared with density measurements. In normal pancreas, no significant difference in perfusion values was observed between head, body, and tail of the pancreas. Mean organ values were 76 mL/100 g/min, 16 mL/100 g, and 28 mL/100 g/min for BF, BV, and PS, respectively. Compared with the normal pancreas, a 60 percent reduction in BF and BV was observed in the tumor tissue. Perfusion values gradually increased toward the tumor rim. Necrotic tumor areas were identified in 25 percent of patients. No significant differences were observed when comparing normal pancreas and healthy pancreatic tissue in

adenocarcinoma patients. The feasibility of whole-tumor perfusion imaging using 128-slice CT was demonstrated in patients with pancreatic adenocarcinoma. Perfusion CT provides additional information compared with image assessment based on density measurements (Hounsfield units) and allows noninvasive assessment of vascularization in the tumor tissue [292].

Size of tumor

Pancreatic cancer primary tumor size measurements are often discordant between computed tomography (CT) and pathologic specimen after resection. Dimensions of the primary tumor are increasingly relevant in an era of highly conformal radiotherapy. It was retrospectively evaluated 97 consecutive patients with resected pancreatic cancer at two Boston hospitals. All patients had CT scans before surgical resection. Primary endpoints were maximum dimension (in millimeters) of the primary tumor in any direction as reported by the radiologist on CT and by the pathologist for the resected gross fresh specimen. Endoscopic ultrasound (EUS) findings were analyzed if available. Of the patients, 87 (90 %) had preoperative CT scans available for review and 46 (47 %) had EUS. Among proximal tumors (n=69), 40 (58 %) had pathologic duodenal invasion, which was seen on CT in only 3 cases. The pathologic tumor size was a median of 7 mm larger compared with CT size for the same patient (range, -15 to 43 mm), with 73 patients (84 %) having a primary tumor larger on pathology than CT. Endoscopic ultrasound was somewhat more accurate, with pathologic tumor size being a median of only 5 mm larger compared with EUS size (range, -15 to 35 mm). It was concluded that computed tomography scans significantly under-represent pancreatic cancer tumor size compared with pathologic specimens in resectable cases. It was proposed a clinical target volume expansion formula for the primary tumor based on our data. The high rate of pathologic duodenal invasion suggests a risk of duodenal under-coverage with highly conformal radiotherapy [293].

CT versus MRI

To intraindividually compare gadoxetic acid-enhanced magnetic resonance (MR) imaging with contrast material-enhanced multi-detector row computed tomography (CT) in detection of pancreatic carcinoma and liver metastases a study included 100 patients (53 men, 47 women; mean age, 68 years) consisting of 54 patients with pathologically confirmed pancreatic carcinoma (mean size, 33 mm) and 46 without a pancreatic lesion. Sixty-two liver metastases (mean size, 10 mm) in 15 patients with pancreatic carcinoma were diagnosed at pathologic examination or multimodality assessment. Three readers blinded to the final diagnosis interpreted all MR (precontrast T1- and T2-weighted and gadoxetic acid-enhanced dynamic and hepatocyte phase MR images) and tetraphasic dynamic contrast-enhanced CT images and graded the presence (or absence) of pancreatic carcinoma and liver metastasis on patient-by-patient and lesion-by-lesion bases. Receiver operating characteristic analysis, McNemar test, and Fisher test were performed to compare the diagnostic performance of CT and MR imaging. No significant differences were observed between CT and MR images in depiction of pancreatic carcinoma. However, MR imaging had greater sensitivity in depicting liver metastasis than did CT for two of the three readers in the MR imaging-versus-CT analysis (85 % vs 69 %) and for all three readers in the lesion-by-lesion analysis. It was thus concluded that gadoxetic acid-enhanced MR imaging was equivalent to dynamic contrast-enhanced CT in depicting pancreatic carcinoma and had better sensitivity for depicting liver metastases, suggesting the usefulness of gadoxetic acid-enhanced MR imaging for evaluation of patients with pancreatic carcinoma [294].

PET-CT

The aim of one study was to determine the negative predictive value of positron emission tomography (PET)/computed tomography (CT) in patients with lesions suggestive of pancreatic cancer. A retrospective review from 2005 to 2008 of all patients who underwent a PET/CT to evaluate a lesion suggestive of pancreatic cancer based on prior imaging. One hundred eighty-four patients underwent PET/CT, of which 60 patients had a negative PET

scan. Of these 60 patients, 56 patients (30 women, 26 men) had endoscopic ultrasound-guided fine-needle aspiration or surgical pathology for clinical correlation. The negative predictive value of PET/CT was 75 percent. Eighteen patients had a benign lesion, 24 patients had a premalignant lesion, and 14 patients had a malignant lesion. In the cystic group, 72 percent of the PET/CT-negative lesions were premalignant compared with the solid group that was only 6 percent. This was in contrast to the solid group, where 65 percent was malignant versus 7 percent in the cystic group. Two of 14 patients with malignancy had metastatic disease. It was concluded that the negative predictive value of PET/CT in pancreatic lesions suggestive of pancreatic cancer was 75 percent. A negative PET/CT does not exclude pancreatic cancer, and further workup of these PET-negative lesions is warranted [295].

Measurements of pancreatic perfusion

The objective of one study was to demonstrate the feasibility of pancreatic perfusion computed tomography (CT) and review pancreatic perfusion measurements by various imaging modalities. Dynamic CT data from 8 patients (4 men; mean age, 65 years) with normal pancreas were analyzed using 2 analytical models: the maximum-slope and compartment-model methods. Literature search was also performed. Although the perfusion value estimated by the maximum-slope method (88 mL/min per 100 mL) was significantly smaller than that of the compartment-model method (127 mL), there was a linear correlation between them. In the literature review, 15 studies that reported the absolute values of normal pancreatic perfusion, by using perfusion CT, dynamic magnetic resonance imaging, hydrogen gas clearance method, and $^{15}\text{O-H}_2\text{O}$ -positron emission tomography were found. The reported mean values of normal pancreatic perfusion ranged from 38 to 356 mL/min per 100 mL, and there was a great deal of individual variation. It was concluded that perfusion CT may provide reliable perfusion measurements of the pancreas, and the normal value was estimated at around 100 mL/min per 100 mL with a great deal of individual variation. The maximum-slope method may provide a lower perfusion value compared with the compartment-model method [296].

MRI

To prospectively determine whether dynamic contrast material-enhanced (DCE) magnetic resonance (MR) quantitative parameters correlate with fibrosis and microvascular density (MVD) in malignant and benign solid pancreatic focal lesions and nontumoral pancreatic tissue a study was performed. DCE MR was performed in 28 patients with surgically resectable focal pancreatic lesions. DCE MR quantitative parameters derived from one-compartment (OC) (transfer rate constant $[K(\text{trans})]$ and distribution fraction $[f]$) and two-compartment (TC) ($K(\text{trans})$, tissue volume fraction occupied by extravascular extracellular space $[v(i)]$, and tissue volume fraction occupied by vascular space $[v(p)]$) pharmacokinetic models were correlated with fibrosis content and MVD counts in focal lesions and nontumoral tissue (Spearman correlation coefficient, SCC). Pharmacokinetic parameters were compared (Mann-Whitney test) between tumoral and nontumoral tissue. Diagnostic performance of DCE MR fibrosis detection was assessed (receiver operator characteristic curve analysis). $K(\text{trans})$ OC and $K(\text{trans})$ TC were significantly lower in primary malignant tumors compared with benign lesions and nontumoral pancreatic tissue downstream and upstream; f and $v(i)$ were significantly higher in primary malignant tumors compared with nontumoral pancreatic tissue downstream. Fibrosis was correlated negatively with $K(\text{trans})$ OC and $K(\text{trans})$ TC and positively with f and $v(i)$. MVD was positively correlated with f and $v(i)$ but not with $K(\text{trans})$ OC and $K(\text{trans})$ TC. Sensitivity and specificity for fibrosis detection were 65 percent (24 of 37) and 83 percent (10 of 12) for $K(\text{trans})$ OC (cutoff value, 0.35/min) and 76 percent (28 of 37) and 83 percent (10 of 12) for $K(\text{trans})$ TC (cutoff value, 0.29 min/min), respectively. It was concluded that quantitative DCE MR parameters, derived from pharmacokinetic models in malignant and benign pancreatic solid lesions and nontumoral pancreatic tissue, were significantly correlated with fibrosis and MVD [297].

PET

Intact antibodies are poor imaging agents due to a long serum half-life (10-20 d) preventing adequate contrast between the tumor and surrounding blood. Smaller engineered antibody fragments overcome this problem by exhibiting shorter serum half-lives (4-20 h). The diabody (55 kDa) is the smallest antibody fragment, which retains the bivalency of the intact antibody. Our goal was to develop and characterize the anti-CA19-9 diabody fragment and determine its ability to provide antigen specific imaging of pancreas cancer. The diabody DNA construct was created by isolation of the variable region genes of the intact anti-CA19-9 antibody. Diabody expression was carried out in NS0 cells and purified using HPLC from supernatant. Specific antigen binding was confirmed with flow cytometry and immunofluorescence. Radiolabeled diabody was injected into mice harboring an antigen positive xenograft (BxPC3 or Capan-2) and a negative xenograft (MiaPaca-2). MicroCT and MicroPET were performed at successive time intervals after injection. Radioactivity was measured in blood and tumor to provide objective confirmation of the microPET images. Immunofluorescence and flow cytometry showed specific binding of the anti-CA19-9 diabody. Pancreas xenograft imaging of BxPC3/MiaPaca-2 and Capan-2/MiaPaca-2 models with the anti-CA19-9 diabody demonstrated an average tumor:blood ratio of 5.0 and 2.0, respectively, and an average positive:negative tumor ratio of 11 and 6, respectively. With respect to the tumor:blood ratio, these data indicate five times and two times more radioactivity in the tumor than in the blood yielding adequate contrast between tumor tissue and background (i.e. blood) to create the representative microPET images. It was successfully engineered a functional diabody against CA19-9, a tumor antigen present on the vast majority of pancreas cancers. Additionally, it was demonstrate high contrast antigen specific microPET imaging of pancreas cancer in xenograft models [298].

Fine needle aspiration

A retrospective cohort study analyzes the potential risks associated with preoperative fine needle aspiration (FNA) biopsy guided by endoscopic ultrasonography (EUS) in patients undergoing distal pancreatectomy. Excluding 204 patients with acute or chronic pancreatitis and those with previous pancreatic resections, 230 consecutive patients with primary pancreatic neoplasms underwent elective distal pancreatectomy between 2002 and 2009. The most common indications were adenocarcinoma (28 %), intraductal papillary mucinous neoplasm (IPMN; 20 %), and endocrine neoplasms (17 %). Two-way statistical comparisons were performed between patients who did (EUS(+)) or did not (EUS(-)) undergo preoperative EUS-FNA. Distal pancreatectomy was performed open in 118 patients (56 %) and laparoscopically in 102 patients (44 %). No differences were observed in age, gender, American Society of Anesthesiologists class, operative time, or blood loss between the EUS(+) (n=179) and EUS(-) (n=51) groups. Splenectomy was performed in 162 patients (70 %) and was more common in the EUS(+) group. With the exception of adenocarcinoma (n=57, 32 %) EUS(+) versus (n=6; 12 %) EUS(-); the final pathologic diagnosis did not differ significantly between the EUS groups. Postoperative complications were more common in the EUS(+) patients with cystic neoplasms (43 % vs 16 % EUS(-)). EUS-FNA caused pancreatitis in 2 patients preoperatively. No differences in overall or recurrence-free survival were noted between cancer patients in the EUS groups. Patterns of tumor recurrence were not associated with EUS-FNA. Preoperative EUS-FNA is not associated with adverse perioperative or long-term outcomes in patients undergoing distal pancreatectomy for solid neoplasms of the pancreas. The potentially detrimental long-term impact of preoperative EUS-FNA in patients with resectable pancreatic adenocarcinoma was not observed, but will require additional study [299].

Liquid-based cytology

To compare results of liquid-based cytology (LBC) and the conventional smear method (SMEAR) when performing endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for lesions of suspected pancreatic malignancy without an on-site cytopathologist. Fifty-eight patients were prospectively enrolled between July and December 2009. Aspirates obtained from the first needle pass were randomized either to SMEAR or LBC. Another sample from the second needle pass was allocated to the other method. The rest of the aspirates from the third or later needle passes were used for SMEAR. Diagnostic accuracy was compared and related factors were pursued. Although both methods were 100 percent specific, LBC was inferior to SMEAR in terms of sensitivity, negative predictive value, and accuracy. However, LBC provided correct diagnoses in 2 out of 3 cases of false negatives for malignancy by SMEAR in which blood was highly contaminated. Although no factor was identified for LBC, low blood contamination and more than 3 needle passes were related with accurate diagnosis in SMEAR. LBC was less accurate than SMEAR when performing pancreatic EUS-FNA without an on-site cytopathologist. However, LBC might serve as a good complement to SMEAR if blood contamination is profound [300].

Monoclonal antibodies in pancreatic juice

Pancreatic cancer (PC) has a poor clinical prognosis with a <10 percent 5-year survival rate. Because there are no specific biomarkers of PC, it is difficult to detect small PC tumors and most patients are diagnosed at an advanced stage. Specific biomarkers are useful tools for the early detection of cancer. However, PC-related biomarkers, such as CA19-9 lack specificity and sensitivity. In this study, we took an immunological approach to establish novel monoclonal antibodies (mAbs) specific for the pancreatic juice from PC patients, which would be potentially useful in the diagnosis of PC. Mice were immunized by subtractive immunization using mixed pancreatic juices from chronic pancreatitis and PC patients as the tolerogen and the immunogen, respectively. After screening by Western blotting, four mAbs were obtained: 2P-1-2-1, 2P-1-17-1, 6P-3-2-4 and 7P-9-11-6. The mAb 2P-1-2-1 showed reactivity against the tolerogen at 115 and 120 kDa, but only the 120-kDa antigen was also reactive to the immunogen. The mAb 2P-1-17-1 showed an intense smear reactivity at ~150 kDa against the immunogen. Finally, the mAbs 6P-3-2-4 and 7P-9-11-6 showed PC-specific reactivity to the immunogen at >250 kDa and at ~70 kDa, respectively. We propose that investigation of pancreatic juice samples with these mAbs may enable us to perform reliable differential diagnosis of benign and malignant diseases. Furthermore, we demonstrated that subtractive immunization is a useful method for producing mAbs specific for the pancreatic juice from PC patients [301].

Prognostic factors

To identify prognostic factors in patients with metastatic pancreatic adenocarcinoma the relationship between patient characteristics and outcome was examined by multivariate regression analyses of data from 409 consecutive patients with metastatic pancreatic adenocarcinoma who had been treated with a gemcitabine-containing regimen, and it was stratified the patients into three risk groups according to the number of prognostic factors they had for a poor outcome. A validation data set obtained from 145 patients who had been treated with agents other than gemcitabine was analyzed. The prognostic index was applied the each of the patients. The multivariate regression analyses revealed that the presence of pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value significantly contributed to a shorter survival time. The patients were stratified into 3 groups according to their number of risk factors, and their outcomes of the 3 groups were significantly different. When the prognostic index was applied to the validation data set, the

respective outcomes of the 3 groups were found to be significantly differed from each other. It was concluded that pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value are important prognostic factors for patients with metastatic pancreatic adenocarcinoma [302].

The Estimation of Physiologic Ability and Surgical Stress score was designed to predict postoperative morbidity and mortality in general surgery. One study aimed to evaluate its use and accuracy in estimating postoperative outcome after elective pancreatic surgery. Between 2002 and 2007, approximately 304 patients requiring pancreatic resection at our institution were recorded prospectively and evaluated retrospectively. The patients' preoperative risk score, surgical stress score (SSS), and comprehensive risk score (CRS) were calculated and compared with the severity of postoperative morbidity, where mortality was regarded as the most severe postoperative complication. Observed and predicted mortality rates were 2.9 percent and 2.0 percent, respectively. Mean CRS was higher in patients who died than in patients that survived, but this difference was not statistically significant. Preoperative risk score, SSS, and CRS did not differ between patients with and without complications. Estimation of Physiologic Ability and Surgical Stress particularly underpredicted morbidity in patients with a CRS between 0.0 and less than 0.5. It was concluded that The Estimation of Physiologic Ability and Surgical Stress scoring system is an ineffective predictor of complications after pancreatic resection. Further refinements to the score calculation are warranted to provide accurate prediction of immediate surgical outcome after pancreatic surgery [303].

Serum profiling for prognosis

One study evaluated the usefulness of electrospray mass spectrometry to distinguish sera of early-stage pancreatic cancer patients from disease-free individuals. Sera peak data were generated from 33 pancreatic cancer patients and 30 disease-free individuals. A "leave one out" cross-validation procedure discriminated stage I/II pancreatic cancer versus disease-free sera with a p value <.001 and a receiver-operator characteristic curve area value of 0.85. Predictive values for cancer stage I/II test efficiency, specificity, and sensitivity were 78 percent, 77 percent, and 79 percent, respectively. These studies indicate that electrospray mass spectrometry is useful for distinguishing sera of early-stage pancreatic cancer patients from disease-free individuals [304].

Early markers for pancreatic cancer

Pancreatic cancer (PC) is a highly lethal malignancy with near 100 percent mortality. This is in part due to the fact that most patients present with metastatic or locally advanced disease at the time of diagnosis. Significantly, in nearly 95 percent of PC patients there is neither an associated family history of PC nor of diseases known to be associated with an increased risk of PC. These groups of patients who comprise the bulk of PC cases are termed as "sporadic PC" in contrast to the familial PC cases that comprise only about 5 percent of all PCs. Given the insidious onset of the malignancy and its extreme resistance to chemo and radiotherapy, an abundance of research in recent years has focused on identifying biomarkers for the early detection of PC, specifically aiming at the sporadic PC cohort. However, while several studies have established that asymptomatic individuals with a positive family history of PC and those with certain heritable syndromes are candidates for PC screening, the role of screening in identifying sporadic PC is still an unsettled question. The present review attempts to assess this critical question by investigating the recent advances made in molecular markers with potential use in the early diagnosis of sporadic PC – the largest cohort of PC cases worldwide. It also outlines a novel yet simple risk factor based stratification system that could be potentially employed by clinicians to identify those

individuals who are at an elevated risk for the development of sporadic PC and therefore candidates for screening [305].

Growth rate

It was reported a case of advanced stage pancreatic cancer with multiple remote metastases to the liver and bones at the time of initial diagnosis. The cancer was observed over the course of 5 months by multidetector row contrast medium-enhanced computed tomography (MDCT). Most pancreatic cancers are unresectable at the time of diagnosis. In this patient, MDCT at 6-month intervals has been continued for the past 5 years as a screening for pancreatic malignancy; however, he developed pancreatic cancer with multiple liver and bone metastases within 5 months after a complete examination by MDCT with negative results. It was speculated that complete examinations at 3-month intervals were needed to find the tumors in their early stages in this patient [306].

PANCREATIC CANCER SURGERY

Organisation of surgical care

High volume

High-volume institutions are associated with improved clinical outcomes for pancreatic cancer. This study investigated the impact of centralizing pancreatic cancer surgery in the south of the Netherlands. All patients diagnosed in the Eindhoven Cancer Registry area in 1995-2000 (precentralization) and 2005-2008 (implementation of centralization agreements) with primary cancer of the pancreatic head, extrahepatic bile ducts, ampulla of Vater or duodenum were included. Resection rates, in-hospital mortality, 2-year survival and changes in treatment patterns were analysed. Multivariable regression analyses were used to identify independent risk factors for death. Some 2129 patients were identified. Resection rates increased significantly from 19.0 to 30.0 percent. The number of hospitals performing resections decreased from eight to three, and the annual number of resections per hospital increased from two to 16. The in-hospital mortality rate dropped significantly, from 24.4 to 3.6 percent and was zero in 2008. The 2-year survival rate after surgery increased from 38.1 to 49.4 percent, and the rate irrespective of treatment increased from 10.3 to 16.0 percent. There was no improvement in 2-year survival in non-operated patients. After adjustment for relevant patient and tumour factors, those undergoing surgery more recently had a lower risk of death (hazard ratio 0.70, 95 % confidence interval 0.51 to 0.97). Changes in surgical patterns seemed largely to explain the improvements. High-quality care can be achieved in regional hospitals through collaboration. Centralization should no longer be regarded as a threat by general hospitals but as a chance to improve outcomes in pancreatic cancer [327].

Evidence-based hospital referral (EBHR) is a Leapfrog group quality metric based primarily on hospital procedural volume. It has yet to be determined if EBHR has led to regionalized surgical care and whether it has improved patient outcomes. It was conducted a before and after cohort study of 13,157 adults (1994 to 2007) who underwent pancreatic or esophageal resection or abdominal aortic aneurysm (AAA) repair in Washington State. Adjusted mortality, readmission, and complication rates were assessed before and after EBHR was introduced. Hospitals meeting an EBHR volume metric in any year ranged from 2 to 6. Comparing before and after 2001 (2004 for pancreatic resection), the proportion of patients treated at hospitals meeting the EBHR volume metric for a given procedure increased for pancreatic (59 % vs 76 %) and esophageal resection (42 % vs 59 %), but was similar for AAA repair (16 % vs 18 %). In general, rates of adverse events were lower at hospitals meeting an EBHR volume metric. However, across Washington State and at non-EBHR

centers, rates of mortality, readmission, and complications generally did not improve in the 7 years after introduction of the EBHR initiative. It was concluded that although a greater proportion of pancreatic or esophageal resections were performed at hospitals meeting a given EBHR volume metric in the 7 years after Leapfrog, this shift had a negligible impact on outcomes across Washington State. It remains to be determined why regionalization for AAA repair has not occurred and why regionalization trends in pancreatic and esophageal surgery have not had the intended impact of improving overall safety outcomes [307].

Pancreatic resection can be performed safely in the community-based hospital setting only when appropriate systems are in place for patient selection and preoperative, operative, and postoperative care. Pancreatic surgery cannot be performed optimally without considerable investment in, and coordination of, multiple departments. Delivery of high-quality pancreatic cancer care demands a rigorous assessment of the hospital structure and the processes through which this care is delivered; however, when a hospital makes the considerable effort to establish the necessary systems required for delivery of quality pancreatic cancer care, the community and hospital will benefit substantially [308].

The Netherlands

Centralization of pancreatic surgery in high-volume hospitals is under debate in many countries. In the Netherlands, the annual incidence of pancreatic cancer is around 1700 new cases of pancreatic cancer and around 440 cases of extra hepatic bile duct cancer [source: Netherlands Cancer Registry]. A resection is done in approximately 15 percent of the cases, resulting in 300 pancreatic resections for malignant disease each year. For more than a decade, there is an ongoing debate for minimal volume standards for pancreatic resections. However, despite the plea for centralization, little had changed in referral patterns or postoperative mortality in the period 1994–2004. The Dutch Healthcare Inspectorate considers a minimal volume standard for pancreatic resections, but already does demand a minimal volume for esophageal resections. However, although many studies on the volume outcome relationship for pancreatic surgery exist, reports showing actual improvement of quality of care after centralization have only been scarce. In the western part of the Netherlands, 9 hospitals are affiliated with the Comprehensive Cancer Centre West (CCCW), 1 of the 8 comprehensive cancer centers in the country. In 2001 the professional network of surgical oncologists (PNSO) in the region formulated quality standards for hospitals performing pancreatic surgery (shown in the frame). Furthermore, they declared the intention to centralize pancreatic surgery after a period of monitoring. In 2005 the PNSO agreed to centralize all pancreatic surgery in 2 centers from January 1, 2006. The aim of one study was to evaluate whether centralization of pancreatic surgery has improved clinical outcomes and has changed referral patterns. Quality criteria for pancreatic surgery formulated by the PNSO of the CCCW in the Netherlands included:

- new patients are preoperatively and postoperatively discussed in a multidisciplinary board with a gastroenterologist and a radiologist
- all patients are operated on by an experienced surgeon
- the hospital has an intensive care unit, intervention radiology, and gastroenterology department
- all patients are operated on by two surgeons together

Data of the Comprehensive Cancer Centre West (CCCW) of all 249 patients who had a resection for suspected pancreatic cancer between 1996 and 2008 in the western part of the Netherlands were analyzed. Outcomes of pancreatic resections in 3 time periods were compared: 1996-2000, 2001-2005, and 2006-2008. In the first period from 1996 till 2000, no quality control for pancreatic surgery was performed in the region. In 2001, quality standards were implemented and from 2006 pancreatic surgery was centralized in 2 hospitals. Outcome was assessed using 30-day mortality, 90-day survival, 1-year survival, and 2-year survival and the number of evaluated lymph nodes. Survival was calculated as the difference

between date of surgery, or – if not available – the date of confirmed diagnosis (which is usually the same as the date of surgery), and, either the date of death, or the date of last patient follow-up. Follow-up of patients was completed until January 1, 2010. For the period 2006–2008, postoperative complications, length of stay, length of ICU admission, and margin status were also analyzed. In addition, the differences in referral pattern were analyzed. From 2006, all pancreatic surgery was centralized in 2 hospitals. From 1996 until 2005 pancreatic surgery was performed in all CCCW-affiliated hospitals. The mean annual hospital volume of oncologic pancreatic resections was 1.7 in 1996–2000 and 2.0 in 2001–2005. Since January 1, 2006, all pancreatic surgery was centralized in 2 hospitals. The mean annual hospital volume increased to 23. After centralization, the percentage of patients receiving surgical treatment for pancreatic cancer increased, from 14.3 to 18.4 percent. The proportion of patients who are living in the CCCW region and had surgery within the region increased from 55 to 69 percent. From 1996 to 2008 in the CCCW region there were no significant differences in patient age, tumor stage, and histology. In the latter period, more patients had a tumor located in the pancreas and chemotherapy use increased from 2 percent in 1996–2000, to 24 percent in 2006–2008. The 30-day mortality fell from 8 percent in the first period to 0 percent and 2 percent in the latter periods. Testing of statistical significance was not feasible because of low numbers. Of all patients with a malignant tumor, the observed 90-day survival significantly improved from 88 to 96 percent, and the 2-year survival from 39 to 55 percent. The 2-year survival first dropped from 38 percent to 28 percent in the first two time periods and then significantly improved to 49 percent in the latest period. The median number of evaluated lymph nodes increased significantly from median 2 to median 7 lymph nodes examined. There was no significant change in observed overall survival. In univariate analysis, risk of death was associated with higher age, a tumor located in the pancreas, stage III and IV, adenocarcinoma of the pancreas, and diagnosis in the early periods. After adjustment for age, tumor location, histology, stage, and adjuvant therapy, a significant association between the latest period of diagnosis and a lower risk of death was seen (hazard ratio 0.50; 95 % confidence interval 0.34 to 0.73). In the period 2006–2009, in total 213 patients underwent pancreatic surgery in the 2 high-volume hospitals. Almost 25 percent of all pancreatic surgery was done for benign diagnosis (53 of 213). Most patients had comorbidity (63 %) and were classified as ASA II (62 %) or higher (15 %). The Whipple and the PPPD procedure were the most performed procedures (49 %). The postoperative mortality was 3.3 percent (7 of 213) and 38 percent (82 of 213) had postoperative complications. Reintervention was carried out in (18 of 213) 9 percent of all patients. The median length of stay was 10 days, and the median stay at the ICU was 1 day. The median interval between first contact and surgery was 22 days. Of all patients who had pancreatic surgery for a malignant diagnosis, 115 of 160 (72 %) had tumor-free margins (R0), 29 of 160 (18 %) had microscopic margin involvement (R1), and 1 patient had macroscopic margin involvement (R2). For 15 of 160 (10 %) the margin status was unknown. The study shows thus that after centralization of pancreatic surgery, the survival of patients with pancreatic malignancies actually improved. The percentage of patients who received surgical treatment for pancreatic cancer increased from 14 to 18 percent. After adjusting for differences in age, tumor stage, location, histology, and adjuvant treatment, a strong association between surgery after centralization and improved survival was shown (HR 0.50; 95 % confidence interval 0.34 to 0.73). In addition, after centralization a higher proportion of patients with pancreatic cancer received surgery. It was expected that since centralization, more patients who had tumor invasion in the venal portal wall had more extensive resections, including resection of the vessel wall. However, this improvement can be attributed to the centralization: more experienced surgeons could also have more experience with more extensive resections. Also, pancreatic surgery for benign pathology does contribute to the experience of the surgeon and the hospital. In the latest period, pancreatic surgery was performed in 25% of the cases because of benign diagnoses. It is expected that including benign diagnosis could have had an additional effect on the effect of centralization. To date there are several studies, reporting the association of concentration of pancreatic care and clinical outcomes. However, most did not evaluate centralization as an intervention, but

described the concentration of care over time. All studies are based on large administrative databases. In-hospital mortality was the outcome parameter in all studies, but only a few were risk adjusted. However, awareness on quality assurance could have had an intrinsic effect on the practice patterns and the dedication of the surgeons and thus have impact on the quality of care, which is known as the Hawthorne effect. At last, the improved survival could have been the result of other improvements in the diagnosis, surgical technique, or postoperative care. However, at a national level, no improvement in overall survival of pancreatic cancer during our study period was observed in the Netherlands (source: Netherlands Cancer Registry, available at www.ikcnet.nl). Although this includes both resected and unresected patients, it can be expected that general improvements in the management of pancreatic cancer would have led to an improved survival at a national level. It is suggested that the beneficial effect of centralization can be explained by better facilities in high-volume centers and more experience of the surgical team, leading to fewer complications, and better treatment adjusted to the patient. These facilities include specialized diagnostic procedures, anesthetic and postoperative care, radiologic and endoscopic interventions, early recognition and treatment of complications, multidisciplinary teams, knowledge of nutrition, and so forth. The evidence for better outcome of complex, low-volume surgical procedures in high-volume centers and the large disparities in quality of care between high- and low-volume centers have fueled the discussion about centralization. Volume is considered a proxy for high quality of care, and volume standards are recommended to improve patient outcomes. However, a minimum volume standard cannot be identified. In conclusion, the study shows that centralization has resulted in improved clinical outcomes of patients who underwent pancreatic surgery for a malignancy. Centralization was realized by agreement of the regional network of surgical oncologists and did not require major structural changes in organization, nor did it affect the accessibility of the health care. These results are encouraging and show how centralization initiatives can actually improve quality of care in a straightforward way [309].

Many studies have shown lower mortality and higher survival rates after pancreatic surgery with high-volume providers, suggesting that centralization of pancreatic surgery can improve outcomes. The methodological quality of these studies is open to question. One study involved a systematic review of the volume-outcome relationship for pancreatic surgery with a meta-analysis of studies considered to be of good quality. A systematic search of electronic databases up to February 2010 was performed to identify all primary studies examining the effects of hospital or surgeon volume on postoperative mortality and survival after pancreatic surgery. All articles were critically appraised with regard to methodological quality and risk of bias. After strict inclusion, meta-analysis assuming a random-effects model was done to estimate the effect of higher surgeon or hospital volume on patient outcome. Fourteen studies were included in the meta-analysis. The results showed a significant association between hospital volume and postoperative mortality (odds ratio 0.32, 95 percent confidence interval 0.16 to 0.64), and between hospital volume and survival (hazard ratio 0.79, 95 % confidence interval 0.70 to 0.89). The effect of surgeon volume on postoperative mortality was not significant (odds ratio 0.46, 0.17 to 1.26). Significant heterogeneity was seen in the analysis of hospital volume and mortality. Sensitivity analysis showed no correlation with the extent of risk adjustment or study country; after removing one outlier study, the result was homogeneous. The data did not suggest publication bias [310].

The US

Fueled by a growing number of studies reporting inverse relationships between hospital volume and surgical mortality, there has been considerable interest in the United States during the previous decade in concentrating selected operations in high-volume hospitals. In 2000, it established minimum volume standards for several surgical procedures as part of a broader, value-based purchasing initiative. Whether such efforts have altered referral patterns for high-risk surgery remains uncertain, however. There are still many barriers to regionalization, including patient preferences for local care, financial incentives for smaller

hospitals to retain surgical cases, and lack of access to high-volume centers in some regions. In one study, it was used data from national Medicare claims to evaluate trends in the use of high-volume hospitals for major cancer resections and cardiovascular surgery. It was also examined concurrent trends in operative mortality rates associated with these procedures and the extent to which decreases in mortality could be associated with a concentration of surgical care in high-volume hospitals. It was identified all patients from 65 to 99 years of age who from 1999 through 2008 underwent pancreatectomy, lung resection, esophagectomy, cystectomy, repair of), carotid endarterectomy, and aortic-valve replacement. Each year, hospitals were ranked according to the volume of Medicare patients for each procedure, adjusting for the proportion of Medicare patients covered by fee-for-service plans. In assessing changes in hospital volumes over time, it was sought to distinguish between the effects of “volume creep” (which occurs when more patients who undergo these high-risk procedures are distributed among the same hospitals) and market concentration (which occurs when patients are redistributed to a smaller number of higher-volume hospitals). Operative mortality, determined from the Medicare eligibility file, was defined as death before discharge or within 30 days after the operation. From 1999 through 2008, more than 3.2 million Medicare patients underwent one of eight cancer operations or cardiovascular procedures at hospitals in the United States. Median hospital volumes increased substantially for the four cancer procedures and AAA repair, and to a lesser extent for aortic-valve replacement. For pancreatic resections, increasing hospital volume occurred as a result of both volume creep and market concentration. For example, median hospital volumes increased from 5 cases of pancreatectomy per year to 16, because the total number of Medicare patients undergoing the procedure increased by 50 percent and the number of hospitals performing the procedure decreased by approximately 25 percent (from 1308 to 978). Risk-adjusted operative mortality rates declined significantly for all eight procedures during the 10-year study period. From 1999 through 2000 and from 2007 through 2008, mortality for pancreatectomy declined with 19 percent for pancreatectomy. Higher hospital volumes explained a large portion of the decline in mortality associated with pancreatectomy (67 %). Market concentration explained the majority of this effect. This analysis of national Medicare data thus shows that average hospital volumes in the United States have increased for several high-risk operations, particularly complex cancer resections. In most cases, rising hospital volumes were driven not only by an overall increase in the number of procedures performed nationally but also by a higher concentration of procedures in a smaller number of hospitals. In addition to patients' being referred from lower- to higher-volume centers, hundreds of U.S. hospitals stopped performing major cancer resections. Other studies suggest that trends toward consolidating high-risk cancer resections at high-volume hospitals were under way well before the period of this analysis and, more specifically, before the efforts of the Leapfrog Group, which started in 2000. Trends toward an increasing concentration of procedures in high-volume hospitals were most pronounced for pancreatectomy, esophagectomy, and cystectomy, which are procedures with particularly strong direct relationships between volume and outcome. For most procedures examined in this study, factors other than hospital volume were responsible for trends toward declining mortality. Some of these factors may be specific to the procedure. Technological advances and the use of checklists in the operating room and improvements in perioperative care, particularly intensive care, have most likely enhanced operative safety. In addition, in the wake of the Institute of Medicine study *To Err Is Human*, 33 published in 1999, hospitals may be striving to improve their safety cultures, staffing, and other factors related to adverse outcomes after surgery. Finally, pay-for-performance programs and other efforts by payers to improve hospital compliance with evidence-based practices related to perioperative care may have contributed to improvements in surgical outcomes. Since most such programs have been implemented only recently, however, they cannot explain improvements in mortality starting more than 10 years ago. For a small number of procedures associated with particularly strong direct volume–outcome relationships, such as pancreatectomy and esophagectomy, referral to high-volume centers should continue to be encouraged. For most high-risk procedures, however, strategies such as operating-room checklists, outcomes-

measurement and feedback programs, and collaborative quality-improvement initiatives are likely to be more effective than volume-based referral. Payers, policymakers, and professional organizations should prioritize programs that have the potential to reduce mortality in all contexts [311].

Korea

To assess the relationship between hospital volume and in-hospital mortality of patients undergoing four surgical procedures for gastrointestinal cancers in Korea using the database of the Health Insurance Review and Assessment Service, it was identified 66,201 patients who underwent the four types of gastrointestinal resection during the period 2005-2006. Participating hospitals were divided into five groups according to their surgical volume. The primary outcome was in-hospital mortality, defined as death from any cause before discharge. Multivariate logistic regression analysis was performed to determine the effect of hospital volume on risk-adjusted in-hospital mortality. It was observed a significant relationship between hospital volume and in-hospital mortality rate for patients undergoing the four types of cancer-related gastrointestinal surgeries. The in-hospital mortality rate was lower for high-volume than for low-volume hospitals after adjusting for patient characteristics. The differences between very-high-volume and very-low-volume hospitals ranged from 0.94 to 2.77 percent for the four procedures, with the largest difference observed for pancreatic resection (3.75 % vs 0.98 %). It was concluded that high-volume hospitals had better short-term surgical outcome than low-volume hospitals also in Korea [312].

Management in relation to race

To test whether hospital-based physicians made different intensive care unit and life-sustaining treatment decisions for otherwise identical black and white patients with end-stage cancer and life-threatening hypoxia it was conducted a randomized trial of the relationship between patient race and physician treatment decisions using high-fidelity simulation. It was counterbalanced the effects of race and case by randomly alternating their order using a table of random permutations. Physicians completed two simulation encounters with black and white patient simulator patients with prognostically identical end-stage gastric or pancreatic cancer and life-threatening hypoxia and hypotension, followed by a self-administered survey of beliefs regarding treatment preferences by race. It was conducted within-subjects analysis of each physician's matched-pair simulation encounters, adjusting for order and case effects, and between-subjects analysis of physicians' first encounter, adjusting for case. Measurements included physician treatment decisions recorded during the simulation and documented in the chart and beliefs about treatment preference by race. When faced with a black versus a white patient, physicians did not differ in their elicitation of intubation preferences, intensive care unit, intubation, or initiation of comfort measures only. Physicians believed that a black patient with end-stage cancer was more likely than a similar white patient to prefer potentially life-prolonging chemotherapy over treatment focused on palliation and to want mechanical ventilation for 1 week of life extension, and less likely to want a do-not-resuscitate order if hospitalized. In this exploratory study, hospital-based physicians did not make different treatment decisions for otherwise identical terminally ill black and white elders despite believing that black patients are more likely to prefer intensive life-sustaining treatment, and they grossly overestimated the preference for intensive treatment for both races [313].

Waiting times

Patients frequently voice concerns regarding wait times for cancer treatment; however, little is known about the length of wait times from diagnosis to surgery in the United States. The objectives of one study were to assess changes in wait times over the past decade and to identify patient, tumor, and hospital factors associated with prolonged wait times for initial

cancer treatment. Using the National Cancer Data Base (1995-2005), 1,228,071 patients were identified who underwent resection for nonmetastatic breast, colon, esophageal, gastric, liver, lung, pancreatic, and rectal cancer at 1443 hospitals. Multivariable models were developed to assess factors associated with time to treatment. From 1995 to 2005, the median time from diagnosis to treatment increased for all cancers. The time from diagnosis to treatment was significantly longer at National Cancer Institute Comprehensive Cancer Centers and Veterans' Administration institutions versus community hospitals. On multivariable analysis, patients were significantly more likely to undergo initial treatment > 30 days from diagnosis if older (6 of 8 cancers), black (5 of 8 cancers), had more comorbidities (6 of 8 cancers), had Stage I disease (7 of 8 cancers), or were treated at National Cancer Institute Comprehensive Cancer Centers or Veterans' Affairs institutions (all cancers). It was concluded that wait times for cancer treatment have increased over the last decade. As case loads increase, wait times for treatment are likely to continue increasing, potentially resulting in additional treatment delay [314].

Readmissions

Recommendations from MedPAC that the Centers for Medicare and Medicaid Services (CMS) report upon and determine payments based in part on readmission rates have led to an attendant interest by payers, hospital administrators and far-sighted physicians. To prospectively evaluate predictive factors of hospital readmission rates in patients undergoing abdominal surgical procedures an analysis of 266 prospective treated patients undergoing major abdominal surgical procedures from 2009 to 2010 was performed. All patients were prospectively evaluated for underlying comorbidities, number of preoperative medicines, surgical procedure, incision type, complications, presence or absence of primary and/or secondary caregiver, their education level, discharge number of medications, and discharge location. Univariate and multivariate analyses were performed. Two hundred twenty-six patients were reviewed with 48 (18 %) gastric-esophageal, 39 (14 %) gastrointestinal, 88 (34 %) liver, 58 (22 %) pancreas, and 33 (12 %) other. Seventy-eight (30 %) were readmitted for various diagnoses the most common being dehydration (26 %). Certain preoperative and intraoperative factors were not found to be significant for readmission being, comorbidities, diagnosis, number of preoperative medications, patient education level, type of operation, blood loss, and complications. Significant predictive factors for readmission were age (≥ 69 years), number of discharged medicines (≥ 9 medications), ≤ 50 percent oral intake (52 % vs 23 %), and discharges home with a home health agency (62 % vs 11 %). Readmission rates for surgeons will become a quality indicator of performance. Quality parameters among Home Health agencies are nonexistent, but will reflect on surgeon's performance. Greater awareness regarding predictors of readmission rates is necessary to demonstrate improved surgical quality [315].

Veteran Affairs Hospital

In a time of increasing specialization, academic training institutions provide a compartmentalized learning environment that often does not reflect the broad clinical experience of general surgery practice. This study aimed to evaluate the contribution of the Veterans Affairs (VA) general surgery surgical experience to both index Accreditation Council for Graduate Medical Education (ACGME) requirements and as a unique integrated model in which residents provide concurrent care of multiple specialty patients. Institutional review board approval was obtained for retrospective analysis of electronic medical records involving all surgical cases performed by the general surgery service from 2005 to 2009 at the Nashville VA. Over a 5-year span general surgery residents spent an average of 5 months on the VA general surgery service, which includes a postgraduate year (PGY)-5, PGY-3, and 2 PGY-1 residents. Surgeries involved the following specialties: surgical oncology, endocrine, colorectal, hepatobiliary, transplant, gastrointestinal laparoscopy, and

elective and emergency general surgery. The surgeries were categorized according to ACGME index requirements. A total of 2,956 surgeries were performed during the 5-year period from 2005 through 2009. Residents participated in an average of 246 surgeries during their experience at the VA; approximately 50 cases are completed during the chief year. On the VA surgery service alone, 100% of the ACGME requirement was met for the following categories: endocrine (8 cases); skin, soft tissue, and breast (33 cases); alimentary tract (78 cases); and abdominal (88 cases). Approximately 50 percent of the ACGME requirement was met for liver, pancreas, and basic laparoscopic categories. The VA hospital provides an authentic, broad-based, general surgery training experience that integrates complex surgical patients simultaneously. Opportunities for this level of comprehensive care are decreasing or absent in many general surgery training programs. The increasing level of responsibility and simultaneous care of multiple specialty patients through the VA hospital systems offers a crucial experience for those pursuing a career in general surgery [316].

Costs of for treatment of pancreatic cancer

Despite the fact that pancreatic cancer is the fourth leading cause of cancer-related death, there is little empirical evidence on its direct healthcare costs and, especially, its indirect costs due to loss of production. One study was a retrospective analysis of all patients with pancreatic cancer (excluding endocrine cancer) in the primary catchment area of Lund University Hospital, Sweden, during the period 2005-2007. Detailed information on all diagnostic and therapeutic investigations, interventions, and postoperative course and long-term follow-up was collected, as well as absenteeism from work due to the health problem, from which direct costs were calculated. The indirect costs for loss of production due to sickness and premature death were calculated by the human capital method. A total of 83 patients were included, for an incidence rate of 9.9 patients/100,000 inhabitants. Direct treatment cost per pancreatic-cancer patient was estimated at EUR 16,066 for each patient's remaining lifetime. Hospitalization accounted for the major expenditure – 60 percent of the lifetime treatment cost. Patients with resectable tumor had a mean cost of EUR 19,809; locally advanced disease, EUR 14,899; and metastatic disease, EUR 16,179. Younger patients and men had a higher than average lifetime treatment cost. The loss of productivity was estimated at EUR 287,420 per patient younger than 65 years of age, of which premature mortality accounted for 79 percent. Adding the cost of palliative care estimated in a previous Swedish study, health-care costs and productivity losses for pancreatic cancer would add up to a substantial economic burden for Sweden at large in 2009 (population 9.1 million), between EUR 86 million and EUR 93 million [317].

Costs of staging laparoscopy

Preoperative imaging is often inadequate in excluding unresectable pancreatic cancer. Accordingly, many groups employ staging laparoscopy (SL), although none have evaluated SL after preoperative magnetic resonance imaging (MRI). It was performed a retrospective, indirect cost-effectiveness analysis of SL after MRI for pancreatic head lesions. All MRI scans administered for proximal pancreatic cancer between 2004 and 2008 were reviewed and the clinical course of each patient determined. It was queried a billing database to render average total costs for all inpatients with proximal pancreatic cancer who underwent pancreaticoduodenectomy, palliative bypass or an endoscopic stenting procedure. It was then performed an indirect evaluation of the cost of routine SL. The average costs of hospitalization for patients undergoing pancreaticoduodenectomy, open palliative bypass and endoscopic palliation were: USD 26,122, USD 21,957 and USD 11,304, respectively. The calculated cost of SL without laparotomy was USD 2966 or USD 1538 prior to laparotomy. The calculated cost of treating unresectable disease by outpatient laparoscopy followed by endoscopy was USD 5943. Routine SL would increase the costs by USD 76,967 (4 %).

Staging laparoscopy becomes cost-effective by diverting unresectable patients from operative to endoscopic palliation. Given the paucity of missed metastases on MRI, the yield of SL is marginal and its cost-effectiveness is poor. Future studies should address the utility of SL by both examining this issue prospectively and investigating the cost-effectiveness of endoscopic versus surgical palliation in a manner that takes account of survival and quality of life data [318].

Overview of treatment

Pancreatic adenocarcinoma (PA) is largely incurable, although recent progress has been made in the safety of surgery for PA and in adjuvant and palliative chemotherapy. The purpose of one study was to describe the management of PA in Ontario, Canada. The Pathology Information Management System (PIMS), which uses electronic pathology reporting (E-path), was used to rapidly identify and recruit patients based on a pathologic diagnosis of PA between 2003 and 2006. Patients were mailed questionnaires for additional data. The patient participation rate was 26 percent (351 of 1325). Nonresponders were more likely to be older than 70 years (43 % vs 28 %) and to have received treatment in nonacademic centres (53 % vs 34 %). Fifty-four percent of responders underwent a potentially curative operation, and most (77 %) were 70 years or younger. Completed resections were documented in 83 percent of patients who underwent exploratory surgery with curative intent; 17 percent of patients had unresectable and/or metastatic disease at laparotomy. Of the completed resections, 24 percent were performed in nonacademic centres with a 32 percent positive margin rate; 76 percent were performed in academic centres with a 29 percent positive margin rate. Resections with curative intent were less frequently aborted in academic centres (10 % vs 33 %). Of the patients who responded to a questionnaire, 43 percent received chemotherapy and 7 percent participated in clinical trials. It was concluded that despite using PIMS and E-path, the response rate for this study was low (< 3 0%). Nonresponders were older and more commonly treated in nonacademic centres. Patients undergoing surgery in academic centres had higher resection rates. The rate of adjuvant and palliative chemotherapy was stage-dependent and low [319].

Influence of old age

To evaluate time trends in surgical resection rates and operative mortality in older adults diagnosed with locoregional pancreatic cancer and to determine the effect of age on surgical resection rates and 2-year survival after surgical resection a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) and linked Medicare claims database (1992-2005) was performed. Medicare beneficiaries aged 66 and older diagnosed with locoregional pancreatic cancer (n=9,553), followed from date of diagnosis to time of death or censorship were investigated. Surgical resection rates increased significantly, from 20 percent in 1992 to 29 percent in 2005, whereas 30-day operative mortality rates decreased from 9 percent to 5 percent. After controlling for multiple factors, participants were less likely to be resected with older age. Resection was associated with lower hazard of death, regardless of age, with hazard ratios of 0.46, 0.51, 0.47, 0.43, and 0.35 for resected participants younger than 70, 70 to 74, 75 to 79, 80 to 84, and 85 and older respectively compared with unresected participants younger than 70. With older age, fewer people with pancreatic cancer undergo surgical resection, even after controlling for comorbidity and other factors. The study demonstrated increased resection rates over time in all age groups, along with lower surgical mortality rates. Despite previous reports of greater morbidity and mortality after pancreatic resection in older adults, the benefit of resection does not diminish with older age in selected people [320].

Influence of young age

The objective of this study was to describe the clinicopathological features and longterm outcomes of young Chinese PAC patients. The study reviewed retrospectively 243 Chinese patients who were diagnosed with primary PAC or any of its variants at one hospital from 1990 to 2009. Other histological types of pancreatic tumors were excluded. Patients younger than 50 years on diagnosis were enrolled. Twenty-five patients were identified from the tumor registry and charts. The pathological findings were reviewed individually to assure accuracy of the diagnosis based on the current diagnostic criteria. Among these 25 patients, diabetes mellitus was seen in 2 patients (1 patient with new-onset diabetes). Four of the 25 patients had a history of pancreatic disease. Chronic pancreatitis presented in 1 patient, and an episode of clinically apparent acute pancreatitis had occurred in 3 other patients preceding the diagnosis of PAC. One patient presented with pancreatic cancer 2 years after undergoing a right nephrectomy for renal cell carcinoma (RCC). Eleven patients had a positive smoking history, and 14 patients were nonsmokers. Seventeen patients (68 %) were nondrinker, 3 patients had an occasional habit of alcoholic consumption, and 5 patients had a regular alcoholic drinking history. At the time of diagnosis, all patients had symptoms. Nineteen patients were misdiagnosed on the first presentation. Symptoms or signs included abdominal pain (72 %), jaundice (52 %), weight loss (48 %), anorexia or nausea (36 %), back pain (28 %), generalized fatigue and weakness (24 %), early satiety (12 %), acute pancreatitis (8%), duodenal obstruction (8 %), and steatorrhea (8 %). The common symptoms of young PAC included thus abdominal pain, weight loss, and nausea/vomiting, similar to those in older patients. Hyperbilirubinemia (serum bilirubin, 92 mg/dL) presented in 13 patients, and alkaline phosphatase was increased in 17 patients. Hyperamylasemia and hyperlipasemia occurred in 35 percent and 50 percent of patients, respectively. Carbohydrate antigen 19-9 and carcinoembryonic antigen were measured in 22 patients. Carbohydrate antigen 19-9 (reference range, 0-35 kU/L) and carcinoembryonic antigen (reference range, 0-5 Kg/L) measurements were normal in 23 percent and 68 percent of the patients, respectively. Of the 25 patients, 13 had metastatic diseases on preoperative evaluation. Of the remaining 12 patients undergoing exploratory laparotomy, 10 were surgically resectable at the initial operation, and 2 were unresectable because of peritoneal carcinomatosis or liver metastases. In the whole cohort, metastatic sites included liver (60 %), peritoneum (36 %), lung (8 %), bone (8 %), brain (4 %), skin (4 %), spleen (12 %), malignant ascites (16 %), and malignant pleural effusion (4 %). On the basis of the Kaplan-Meier analysis, the overall 1- and 5-year survival rates of all patients in the study were 28 percent and 4 percent, respectively. The median and mean survival times were 6 and 13 months, respectively. Among the resected patients, 9 patients, to date, had tumor recurrence. The 1- and 5-year survival rates were 40 percent and 10 percent, respectively with a median survival of 10 months. The subgroup of nonresected patients had a median survival of 5 months and a mean survival of 7 months. The longest survivor in the series to date is a patient with stage IB disease who has lived more than 15 years after primary resection. There were no significant effects of resection, chemotherapy, and radiation therapy on survival [321].

Radical surgery

Surgery is the only therapy with potentially curative intention in pancreatic cancer. One analysis aimed to determine prognostic parameters in a patient cohort with resected pancreatic adenocarcinoma with a special focus on the revised R1-definition. Between 2001 and 2009, data from 1071 consecutively resected patients with pancreatic adenocarcinoma were prospectively collected in an electronical database. Parameters tested for survival prediction in univariate analysis included patient, tumor, and resection characteristics as well as adjuvant therapy. The parameters with significant results were used for multivariate

survival analysis. Identified parameters with positive or negative prognostic effect were used to define risk groups and to assess the effects on patient survival. Age, ASA-score, CEA and CA19-9 levels, preoperative insulin-dependent diabetes mellitus, T-, N-, M-, R-, G-tumor classification, advanced disease, and LNR were all significant in univariate analysis, whereas gender, NYHA score, BMI, insurance status, type of surgical procedure, and adjuvant therapy were not. In multivariate analysis, age ≥ 70 years, preoperative insulin-dependent diabetes, CA19-9 ≥ 400 U/mL, T4-, M1- or G3-status, and LNR > 0.2 were independent negative predictors, whereas Tis/T1/T2-status, G1-differentiation, and R0-status (revised definition) were independently associated with good prognosis. Using these risk factors, patients were stratified into 4 risk-groups with significantly different prognosis; 5-year survival varied between 0 percent and 55 percent. Risk stratification resulted in improved survival prognostication within the predominant AJCC IIA and AJCC IIB stages. Thus, a newly defined prognostic profiling including the revised R1-definition discriminates survival of patients with resectable pancreatic adenocarcinoma better than the AJCC staging system, and may be of particular relevance for patient-adjusted therapy in the heterogeneous group of AJCC stage II tumors [322].

Pre-resectional laparoscopy

The aims of one study were to verify whether the selective use of staging laparoscopy can prevent unnecessary laparotomy and to find a surrogate marker for surgical unresectability in patients with potentially or borderline resectable pancreatic cancer. Group A consisted of consecutive 33 patients evaluated between 2005 and 2006 and who directly underwent open laparotomy for planned surgical resection. Group B consisted of consecutive 61 patients evaluated between 2007 and 2009 and of whom 16 patients (26 %) had a staging laparoscopy due to the presence of high-risk markers of unresectability defined as carbohydrate antigen 19-9 level 150 U/mL or greater and tumor size 30 mm or greater. The frequency of unnecessary laparotomies for occult distant organ metastasis was significantly different between groups A and B (18 % and 3 %, respectively). Of 16 patients who underwent staging laparoscopy in group B, 5 patients (31 %) had occult metastases. The multivariate analysis showed that the presence of high-risk markers and extrapancreatic plexus invasion on multidetector-row computed tomography were significant independent risk factors for unresectability. It was concluded that the presence of high-risk markers was associated with surgical unresectability in patients with potentially or borderline resectable pancreatic cancer. The selective use of staging laparoscopy decreased the frequency of unnecessary laparotomy by detecting minute metastases [323].

Reconstruction after pancreatoduodenectomy

Pancreatic fistula (PF) is an important factor responsible for the considerable morbidity associated with pancreaticoduodenectomy (PD). There have been many techniques proposed for the reconstruction of pancreatic digestive continuity to prevent fistula formation but which is best is still highly debated. It was carried out a systematic review and meta-analysis to determine the effectiveness of methods of anastomosis after PD. A full literature search was conducted in the Cochrane Controlled Trials Register Databases, Medline, and other resources irrespective of language. Randomized controlled trials (RCTs) were considered for inclusion. Analyses were carried out using RevMan software. In all, ten RCTs that included a total of 1,408 patients were included. The meta-analysis showed that the PF, postoperative complications, biliary fistula, mortality, reoperation, and length of hospital stay were not statistically different between the pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) groups. The PF, postoperative complications, mortality, and reoperation were not statistically different between the duct-to-mucosa PJ and PJ groups. Binding PJ significantly decreased the PF and postoperative complications compared with conventional PJ. The PF, postoperative complications, and mortality were not statistically

different between ligation of the pancreatic duct without anastomosis versus PJ. It was concluded that no pancreatic reconstruction technique after PD was found to be applicable to all kinds of pancreatic remnants in a systematic review and meta-analysis. Some new approaches such as binding PJ and modified PG will be considered for study in the future [324].

Duct-to-mucosa pancreatojejunostomy

A variety of different techniques are established for the management of the pancreatic remnant after partial pancreaticoduodenectomy. Although pancreatojejunostomy is one of the most favored methods, technical details are still under discussion. It was reported about a series of duct-to-mucosa pancreatojejunostomies with total external drainage of the pancreatic duct. Between 1998 and 2007 257 patients underwent surgical therapy for malignant disease of the pancreas and the periampullary region and for chronic pancreatitis. Of these, 153 partial pancreaticoduodenectomies (85 pylorus preserving resections and 68 Whipple's procedures) were performed. In all of these cases, the pancreatic remnant was drained by a duct-to-mucosa pancreatojejunostomy with external drainage of the pancreatic duct. Presence of postoperative pancreatic fistula (PPF) was defined according to the International Study Group on Pancreatic Fistula (ISGPF). Postoperative mortality was 1.9 percent. The incidence of postoperative pancreatic fistula (PPF) was 20 percent according to the ISGPF criteria. Only one patient required re-laparotomy for complications caused by PPF. Patients with PPF had a significantly longer operation time (7.3 h versus 6.6 h). Incidence of PPF was not influenced by histology. In all cases the fistulas resolved under conservative treatment. Duct-to-mucosa PJ with external drainage is a safe procedure to enteralize the pancreatic stump after partial pancreaticoduodenectomy [325].

End-to-side purse-string suture

Pancreatic fistula is a leading cause of morbidity and mortality after pancreaticoduodenectomy. It was designed a modified technique, by which the pancreatic stump was invaginated into the jejunal loop by purse-string suture. From 2008 18 cases of patients were performed with this modified technique, and the morbidity and mortality were calculated. All cases recovered well from pancreaticoduodenectomy, and none of them occurred pancreatic fistula. The complications included: hemorrhage, wound infection, pulmonary infection, and ascite. Invagination anastomosis by purse-string suture could be performed safely and reduced the leakage rate of pancreatojejunostomy [326].

Comparisons of classical Whipple and PPPD

The standard treatment for resectable pancreatic tumours is either a classic Whipple operation or a pylorus-preserving pancreaticoduodenectomy. It is unclear which of the procedures is more favourable in terms of survival, mortality, complications and quality of life. Several publications have highlighted advantages and disadvantages of the two techniques and the current basis of evidence remains unclear. The objective of one systematic review was to compare the effectiveness of each operation. It was conducted a search on 2006 to identify all RCTs, applying no language restriction. It was searched the following electronic databases: CENTRAL, CDSR and DARE from The Cochrane Library (2006, issue 2), MEDLINE (1966 to 2006) and EMBASE (1980 to 2006). It was handsearched abstracts from 1995 to 2006 from the American Digestive Disease Week (DDW), published in Gastroenterology, and the United European Gastroenterology Week (UEGW), published in Gut. It was considered randomised controlled trials comparing the classic Whipple operation with pylorus-preserving pancreaticoduodenectomy to be eligible if they included patients with periampullary or pancreatic carcinoma. Two authors independently extracted data from the included studies. We used a random-effects model for pooling data. It was compared binary outcomes using odds ratios (OR), pooled continuous outcomes using weighted mean differences (WMD), and used hazard ratios (HR) for meta-analysis of survival. Two authors independently evaluated the methodological quality of included studies according to quality

standards and by using a questionnaire. It was retrieved 1235 abstracts and checked these for eligibility, including seven randomised controlled trials. The critical appraisal revealed vast heterogeneity with respect to methodological quality and outcome parameters. Comparisons of in-hospital mortality (OR 0.49; 95 % confidence interval 0.17 to 1.40), overall survival (HR 0.84; 95 % confidence interval 0.61 to 1.16) and morbidity showed no significant differences. However, it was noted that operating time and intra-operative blood loss were significantly reduced in the pylorus-preserving pancreaticoduodenectomy group. The authors concluded that there is no evidence of relevant differences in mortality, morbidity and survival between the two operations. Given obvious clinical and methodological heterogeneity, future research must be undertaken to perform high-quality randomised controlled trials of complex surgical interventions on the basis of well-defined outcome parameters [328].

Pylorus resecting pancreatoduodenectomy

To determine in a prospective randomized controlled trial (RCT) whether pylorus-resecting pancreatoduodenectomy (PrPD) with preservation of nearly the entire stomach reduces the incidence of delayed gastric emptying (DGE) compared with pylorus-preserving pancreatoduodenectomy (PpPD). Several RCTs have compared PpPD and conventional pancreatoduodenectomy with antrectomy. However, no study has reported the difference between PrPD with preservation of nearly the entire stomach and PpPD. One hundred thirty patients were randomized to preservation of the pylorus ring (PpPD) or to resection of the pylorus ring with preservation of nearly the entire stomach (PrPD). The incidence of DGE was 5 percent in PrPD and 17 percent in PpPD, a significant difference. Delayed gastric emptying was classified into 3 categories proposed by the International Study Group of Pancreatic Surgery. The proposed clinical grading classified 11 cases of DGE in PpPD into grades A (n=6), B (n=5), and C (n=0) and one case in PrPD into each of the 3 grades. The time to peak CO₂ content in the C-acetate breath test at 1, 3, and 6 months postoperatively was significantly delayed in PpPD compared with PrPD (34 ± 25 minutes versus 19 ± 12 minutes, 27 ± 21 minutes versus 17 ± 12 minutes, 27 ± 19 minutes versus 17 ± 13 minutes, respectively). Pylorus-resecting pancreatoduodenectomy and PpPD had comparable outcomes for quality of life, weight loss, and nutritional status during a 6-month follow-up period. The authors concluded that pylorus-resecting pancreatoduodenectomy significantly reduces the incidence of DGE compared with PpPD [329].

Total pancreatectomy

Total pancreatectomy (TP) has been performed rarely in the past because of its high morbidity and mortality. Because outcomes of pancreatic surgery as well as management of pancreatic insufficiency have improved markedly, enthusiasm for TP has increased. Between 1996 and 2008, 65 patients (33 females, 32 males; median age, 63 years) underwent TP at a single, high-volume center. Indications, timing, and perioperative and long-term results were analyzed. Twenty-five patients (39 %) underwent a planned, elective TP and 25 patients underwent a single-stage unplanned TP after an initial partial pancreatectomy that required TP because of intraoperative hemorrhage (n=1) or positive pancreatic resection margin (n=24). The remaining 15 patients (23 %) underwent a 2-stage pancreatectomy for tumor recurrence in the remnant. No completion TP for postoperative complications was performed. There was no mortality; the overall morbidity was 39 percent and the reoperation rate was 5 percent. Overall, 48 percent of patients had intraductal papillary mucinous neoplasms, and 29 percent pancreatic ductal adenocarcinoma. The R1 resection rate was 12 percent. Four of 23 patients (17 %) who underwent single-stage, unplanned TP for positive resection margin had R1 resection (positive retroperitoneal margin). The median follow-up was 34 months. The overall 5-year survival was 71%. No deaths owing to hypoglycemia were observed. Median insulin was 32 U/d, and the median lipase was 80,000 U/d. Thus, TP can be performed safely with no mortality and acceptable

morbidity. Postoperative pancreatic insufficiency can be managed safely. To achieve an R0 during TP, both the resection and retroperitoneal margin should be evaluated intraoperatively. TP is an effective operation in selected patients [330].

In children

Contemporary surgical practice is increasingly dominated by subspecialisation in response to improved outcome from high volume centres, though uncertainties persist for uncommon paediatric procedures. Three paediatric pancreaticoduodenectomies performed over a period of 9 years were evaluated to substantiate their continuing performance by paediatric rather than adult pancreatic surgeons. With ages ranging from 18 months to 8 years old, the mean operating time was 263 minutes, while the average hospital stay was 12 days. There was no perioperative mortality, although complication rate was 100 percent. Re-operation was required in 33 percent. The long term outcome of this small paediatric cohort was comparable to adult series despite the low patient accrual, underscoring the advantages of a multidisciplinary approach afforded by tertiary paediatric institutions for intricate yet infrequent operations in children [331].

Arterial resections

Arterial resection (AR) has traditionally been considered as a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma. The objective of one study was to evaluate if pancreatic resection with AR was worthwhile. Between 1990 and 2008 the records of 26 consecutive patients who underwent a curative-intent pancreatic resection for adenocarcinoma of the pancreas with AR (AR+ group) were matched 1:1 to those of the whole series of pancreatic resection performed in our institution. The final study population (n=52) included two groups of patients: the study group AR+=26 and the control group AR-=26. The 1- and 3-year survival rates were similar in the two groups (66 % and 22 %, median 17 months for the group AR+, versus 50 % and 18 %, median 12 months, for the group AR-. The multivariate analysis showed that: arterial wall invasion at the site of AR, the total number of resected lymph nodes of ≤ 15 , and perineural invasion were independent prognostic factors for survival. It was concluded that pancreatic resections with AR for adenocarcinoma allowed to obtain a 3-survival rate similar to that of a matched group of patients not requiring arterial resection [332].

The majority of pancreatic cancers are diagnosed at an advanced stage. As surgical resection remains the only hope for cure, more aggressive surgical approaches have been advocated to increase resection rates. Institutions have begun to release data on their experience with pancreatectomy and simultaneous arterial resection (AR), which has traditionally been considered a general contraindication to resection. The aim of one meta-analysis was to evaluate the perioperative and long-term outcomes of patients with AR during pancreatectomy for pancreatic cancer. The Medline, Embase, and Cochrane Library and J-East databases were systematically searched to identify studies reporting outcome of patients who underwent pancreatectomy with AR for pancreatic cancer. Studies that reported perioperative and/or long-term results after pancreatectomy with AR were eligible for inclusion. Meta-analyses included comparative studies providing data on patients with and without AR and were performed using a random effects model. The literature search identified 26 studies including 366 and 2243 patients who underwent pancreatectomy with and without AR. All studies were retrospective cohort studies and the methodological quality was moderate to low. Meta-analyses revealed AR to be associated with a significantly increased risk for perioperative mortality (odds ratio 5.04; 95 % confidence interval 2.69 to 9.45) poor survival at 1 year (odds ratio 0.49; 95 % confidence interval 0.31 to 0.78) and 3 years (OR = 0.39; 95 % confidence interval 0.17 to 0.86) compared with patients without AR. The increased perioperative mortality (odds ratio 8.87; 95 % confidence interval 3.40 to 23.13) and lower survival rate at 1 year (odds ratio 0.50; 95 % confidence interval 0.31 to 0.82) was confirmed in the comparison to patients undergoing venous resection. Despite

substantial perioperative mortality, pancreatotomy with AR was associated with more favorable survival compared with patients who did not undergo resection for locally advanced disease. AR in patients undergoing pancreatotomy for pancreatic cancer is associated with a poor short and long-term outcome. Pancreatotomy with AR may, however, be justified in highly selected patients owing to the potential survival benefit compared with patients without resection. These patients should be treated within the bounds of clinical trials to assess outcomes after AR in the era of modern pancreatic surgery and multimodal therapy [333].

Early ligation of the inferior pancreaticoduodenal artery

The ideal surgical procedure for treating pancreatic cancer achieves radical excision in a minimally invasive manner and allows rapid transition to adjuvant chemotherapy. If the afferent artery to the pancreatic head is not ligated until the latter half of the surgery, congestion of the pancreaticoduodenal vein may occur, leading to phleborrhagia and increased intraoperative hemorrhage. Ligation of the afferent artery, i.e., the inferior pancreaticoduodenal artery (IPDA), in the first half of the surgery may prevent the occurrence of hemorrhage due to congestion. Early ligation of the IPDA is also useful in ensuring the success of radical dissection of the plexus around the superior mesenteric artery or the no. 14 lymph node. It has been performed pancreaticoduodenectomies with antecedent IPDA ligation since 2005 and has been found that the percentage of R0 versus R1 and R2 has increased compared with that when standard pancreaticoduodenectomies were performed. Preemptive ligation of the IPDA early in pancreaticoduodenectomy for invasive pancreatic cancer is a useful method for reducing blood loss and achieving R0 resection in a thorough yet efficient manner [334].

Portal vein resection

Portal vein-superior mesenteric vein invasion by pancreatic cancer is down-staged from T4 to T3 in the sixth AJCC/UICC stage based on the concept that PV-SMV invasion is not the result of aggressive behavior but the result of tumor location. However, since the 1990s, there have been many reports showing that PV-SMV invasion has resulted in poor survival. Recently published systematic review of 52 studies with 1646 patients revealed that the median survival time and 5-year survival rate of patients with PV-SMV invasion were 12 months and 6 percent, respectively. They also showed a high rate of lymph node metastasis (67 %), which implies that, by the time a pancreatic cancer involves the PV-SMV, the risk of metastasis is high. Therefore, PV-SMV invasion is not simply a matter of location, but also the location itself is important because the vessel directly enters the liver, which is the most common site of metastasis of pancreatic cancer. However, there are still many other opinions that PV-SMV resection could achieve better survival. As the rationale for PV-SMV resection is to obtain a tumor-free margin, which is known to be a significant prognostic factor, the clinical benefit of PV-SMV resection should be evaluated in patients undergoing R0 resection and in patients with true invasion. However, because pancreatic cancer induces a severe desmoplastic reaction with the surrounding tissue, in some cases, pancreas was not separated from the vessel as if there is cancer invasion. Radiologists usually evaluate vascular invasion, depending on the degree of vascular encasement by the tumor on preoperative imaging studies. If the tumor encases the vessel more than 180 degrees, it is considered as a tumor invasion. Some surgeons used intraportal ultrasonography or angiography to evaluate vascular invasion intraoperatively or preoperatively. The reason for the low cure rate of pancreatic cancer is thus that this tumor easily metastasizes to the liver and infiltrates into the surrounding major vessels such as portal vein (PV), superior mesenteric vein (SMV), hepatic artery, or superior mesenteric artery. With the advances in surgical technique and accumulation of experiences, PV-SMV invasion is not considered to be a contraindication to resection, and synchronous PV-SMV resection is recommended during pancreatoduodenectomy (PD) with or without pylorus-preserving procedures to obtain

a tumor-free margin in the absence of metastatic disease. From the sixth American Joint Committee on Cancer/International Union Against Cancer stage, PV-SMV invasion is categorized as the same stage as peripancreatic infiltration (T3), which is different from the fifth edition (T4). However, PV directly enters the liver, which is the most common site of metastasis of pancreatic cancer. This means that there is a possibility of tumor spreading from the invaded focus of the PV-SMV to the liver. One can find early liver metastasis (within 6 months of margin-negative surgery) not infrequently in patients with a huge mass with PV-SMV total obliteration. It has been reported that a tumor bigger than 5 cm receive no benefit from surgery even after regional pancreatectomy. 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. Pylorus preservation was attempted in all cases unless severe duodenal ischemia, duodenal ulcer, or cancer infiltration into the duodenal bulb was present. Combined resection of the PV-SMV was performed if pancreas was not separated from the vessel. Lymph node dissection included removal of the regional lymph nodes to the right side of the celiac and superior mesenteric artery and removal of all the lymphatic and nerve tissues in the hepatoduodenal ligament. Aortocaval lymph node (a2, b1) dissection was also performed. The mean number of harvested lymph nodes was 31.4 per patient. After surgery, we performed concurrent chemoradiation (CCRT) on all patients without severe medical comorbidities and poor physical status. The depth of vessel invasion was investigated and was categorized into 3 groups: tunica adventitia, media, and intima. Clinicopathologic factors and survival were analyzed. The following factors were analyzed: age, gender, tumor marker, operation modality, blood transfusion, tumor size, tumor stage, lymph node metastasis, histological differentiation, lymphatic invasion, perineural invasion, and vascular invasion including PV-SMV invasion. The cumulative survival rate was calculated by the Kaplan-Meier method. Factors associated with cumulative survival in both univariate and multivariate analyses were identified by the Cox proportional hazard regression analysis. Operative procedures included 16 cases of PD (27 %), 40 cases of PPPD (67 %), and 4 cases of total pancreatectomy (7 %). The mean operation time was 8 hours (range, 5-14 hours), and intraoperative transfusion was required in 17 patients (28 %). Median postoperative hospital stay was 23 days, and 20 patients (33 %) developed postoperative complications. Nineteen patients (32 %) underwent PV-SMV resection including segmental resection with end-to-end anastomosis (n=17) or wedge resection (n=2). In all 60 patients, a tumor-free resection margin (R0) was obtained. The mean tumor size was 3.1 cm (range, 1.5-7.0 cm), and lymph node metastasis was observed in 45 cases (75 %). Tumor classification according to the seventh AJCC/UICC staging system in the 60 patients was as follows: T1/T2/T3 were 3 (5 %)/1 (2 %)/56 (93 %). The histopathologic differentiation was as follows: 5 (8 %) had the well-differentiated type; 40 (67 %), the moderately differentiated type; and 10 (17 %), the poorly differentiated type. The data on tumor differentiation were not available in 5 patients. Perineural, lymphatic, and blood vessel invasions were detected in 54 (90 %), 49 (82 %), and 33 patients (55 %), respectively. Among the 19 patients who underwent PV-SMV resection, histologically true tumor invasion of PV-SMV was observed in 15 patients (79 %), and the remaining 4 patients (21 %) proved to have only fibrous adhesion. The depths of tumor invasion of the PV-SMV were divided into 3 groups: tunica adventitia (n=3), tunica media (n=7), and tunica intima (n=5). The overall 1- and 3-year survival rates in 60 patients who underwent R0 surgical resection were 55 percent and 33 percent, respectively, and the median survival was 14 months. Clinicopathologic factors were analyzed as variables possibly affecting prognosis. Univariate analysis revealed that poorly differentiated tumor, lymphatic invasion, endovascular invasion, PV-SMV invasion, and PV-SMV intima invasion were statistically significant. The depth of PV-SMV invasion showed a deeper invasion led to a poorer survival rate, but had only a marginal significance. By multivariate analysis, poorly differentiated tumor and PV-SMV intima invasion turned out to be independent poor prognostic factors. There were 39 patients

with recurrence, and 32 (82 %) of them had systemic recurrence such as liver metastasis, peritoneal seeding, or lung metastasis. Among the 39 recurred patients, 28 patients were in PV-SMV noninvasion group and 11 in PV-SMV invasion group. Liver metastasis was found in 14 patients in PV-SMV noninvasion group (50 %) and 5 in PV-SMV invasion group (46 %). There was no significant difference between 2 groups. One patient developed PV-SMV resection-related complication, which was PV thrombosis, and she recovered after stent insertion with thrombolysis. There were 2 hospital mortalities (3.3 %); 1 patient died on postoperative day 16 due to superior mesenteric artery pseudoaneurysm rupture, and the other died on postoperative day 279 due to superior mesenteric artery stenosis that resulted in small bowel necrosis followed by sepsis and multiorgan failure. 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 about 20 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 pancreatoduodenectomy for pancreatic adenocarcinoma [335].

Pancreatic head resection with artery and vein en bloc

Curative resection has been shown to be one of the key factors affecting the survival of patients with carcinomas of the head of the pancreas. However, local recurrence is very common, and Esposito and colleagues stated that: "Most pancreatic cancer resections are R1 resections." In 2002, it was developed a new method for en bloc resection of the pancreatic head including the superior mesenteric artery (SMA) and vein (SMV) for pancreatic head carcinoma with portomesenteric invasion, called "augmented regional pancreatoduodenectomy (ARPD)." The technical and general eligibility criteria for ARPD are:

- presumed achievement of R0 status
- tumor infiltration proximal to the SMV and SMA
- tumor respecting the hepatic artery, splenic artery, and celiac trunk and neither hepatic nor paraaortic nodal metastasis

Between 2002 and 2010, 17 patients underwent ARPD in one institution. Postoperative death occurred in 2 patients. One death occurred after full-dose radiotherapy and the other after rupture of an aortic aneurysm. The surgical margins (R0) were histologically negative in 14 patients (82 %). The overall 5-year survival probabilities were 24 percent in R0. Three patients survived more than 5 years. The ARPD procedure has advantages in obtaining sufficient margins at the uncinate and posterior site in patients with pancreatic head carcinoma [336].

En bloc resection av truncus coeliacus

Surgery for locally advanced pancreatic cancer with arterial involvement of the hepatic artery, coeliac trunk and superior mesenteric artery (SMA) is highly controversial. In a retrospective review, the benefits and harms of arterial en bloc resection (AEBR) for pancreatic adenocarcinoma with arterial involvement were analysed. Patients were divided into three groups: 29 patients who had pancreatic resection and AEBR (group 1), 449 who had pancreatic resection with no arterial resection or reconstruction (group 2), and 40 with unresectable tumours who underwent palliative bypass (group 3). Eighteen patients underwent reconstruction of the hepatic artery, eight of the coeliac trunk and three of the

SMA. Additional reconstruction of portal vein was required in 15 patients and of adjacent visceral organs in 19. Perioperative morbidity and mortality rates were higher in group 1 than in group 2. Additional portal vein resection was an independent predictor of morbidity. Median overall survival was similar for groups 1 and 2 (14 vs 16 months), and lower for group 3 (8 months). It was concluded that in selected patients AEHR can result in overall survival comparable to that obtained with standard resection and better than that after palliative bypass. Nevertheless, AEHR is associated with significantly higher morbidity and mortality rates, counterbalancing the overall gain in survival and limiting the overall oncological benefit [337].

LigaSure

Pancreatic surgery requires extensive preparation and tissue dissection. Therefore, LigaSure provides an alternative to conventional dissection techniques. The aim of one study was to describe the feasibility, safety, and cost efficiency of LigaSure in pancreatoduodenectomy. Seven patients underwent surgery with the Ligasure and 7 patients underwent surgery with conventional dissection techniques. The patients were investigated for surgical time, intraoperative blood loss, complications, mortality, duration of hospital stay, and surgery-related costs. Surgical time was 207 minutes in the LigaSure group and 255 minutes in the conventional group. Intraoperative blood loss was 271 and 771 mL, respectively. Other perioperative outcomes were comparable. The respective surgery-related costs averaged EUR 4,125 and EUR 4,931, which was a significant difference. The use of LigaSure in pancreatoduodenectomy seems to be feasible and safe. In addition, it might lead to a reduction in the surgery-related costs [338].

Robotic surgery

Historically, total pancreatectomy (TP) has been considered to be a technically demanding operation characterized by high morbidity and mortality rates. Introduced in the early 2000s, the use of robotic surgery is now being applied to more complex operations, including pancreatic resections. It was reported a preliminary experience with five cases of robotic total pancreatectomy. Patients were placed in a supine position with parted legs and 20-degree reverse Trendelenburg adjustment. Pneumoperitoneum was obtained with the use of a Veress needle in the left hypochondrium to insufflate the abdominal cavity to 14 mm Hg pneumoperitoneum. A first 5 mm trocar was placed under direct vision in the left hypochondrium and used for preliminary visual exploration of the abdominal cavity. A total of 5 trocars were then added along a concave line centered on the right hypochondrium. The first was a 12 mm trocar placed on the right pararectal line for the robotic camera (trocar 1). After this, three 8-mm robotic trocars were inserted into the left upper quadrant (trocar 2), right upper quadrant (trocar 3), and right subcostal area (trocar 4). Finally, a 12 mm port (trocar A) was placed on the left side of the umbilicus for use with the assistant's instruments. The da Vinci surgical robot cart was then brought into a directly cranial position to the patient and docked to the robotic trocars. The stepwise conduct of the operation varied according to indications. In cases with no neoplastic involvement at the pancreatic neck, the operation was divided into 2 parts: a left pancreatectomy (with or without splenic vessel preservation) followed by a pancreaticoduodenectomy. En bloc spleen-preserving total pancreatectomy was performed in one patient with branch duct (head) IMPN associated with dilation of the main pancreatic duct. In this case, the gastrocolic ligament was opened using the harmonic robotic dissector. The left colonic flexure was taken down to expose the inferior edge of the pancreatic body and tail. The right colonic flexure was then taken down and a complete Kocher maneuver performed. The dissection proceeded at the inferior border of the pancreatic head. Following the middle colic vein, the superior mesenteric vein was exposed at the inferior edge of the pancreatic neck. Using the robotic grasper, a tunnel was created under the pancreatic neck and through a gentle dissection with tangential movements in

relation to the vascular axis. A tape was then passed through to achieve traction, and the splenic vein was isolated at the confluence with the portal vein and then taped. The dissection followed at the inferior border of the pancreatic body in a medial-to-lateral fashion. The pancreatic body and tail were then dissected from the splenic vessels, controlling each small branch of the splenic vein and artery to and from the pancreas, with transfixed stitches of nonresorbable 5-0/6-0 suture until the splenic hilum was reached. The dissection of the hepatoduodenal ligament began with a retrograde cholecystectomy, followed by sectioning of the right gastric artery and the gastroduodenal artery between transfixed stitches of polypropylene 4/0. The gastric antrum was transected using a laparoscopic stapler. The first jejunal loop was identified by moving the robotic instruments toward the left hypochondrium. It was then transected 15 cm from the Treitz ligament using an endoscopic stapler. The proximal end was passed behind the superior mesenteric vessels and retracted toward the right side. Once this was complete, the distal pancreas was retracted in the right upper quadrant using the fourth arm instrument. The uncinate process was then detached from the superior mesenteric vessels using the harmonic shears. The retroportal lamina was transected using the harmonic dissector and the pancreaticoduodenal vessels were transfixed using 4/0 and 5/0 polypropylene stitches. Once the dissection was finished, the pneumoperitoneum was stopped and the robotic cart temporarily removed. The specimens were extracted in a plastic bag through a small (6 cm) Pfannenstiel incision, which was then closed. The pneumoperitoneum was restarted and the robotic cart again docked to the robotic ports. During the reconstruction, the first jejunal loop was transposed in the right hypochondrium behind the superior mesenteric vessels. An end-to-side hepaticojejunostomy was then performed using polydioxanone (PDS) 4/0 running sutures for the posterior layer and interrupted PDS 5/0 stitches for the anterior layer. A side-to-side gastrojejunostomy was performed 40 to 50 cm distal to the previous anastomosis using a laparoscopic stapler and running sutures of PDS 3/0. Two drains were left in place close to the gastrojejunostomy and the hepaticojejunostomy. From 2007 to 2010, it was performed 5 robotic total pancreatectomies. Two procedures were spleen-preserving and 3 involved a splenectomy. The overall mean operative time was 456 minutes with a mean surgical blood loss of 310 mL. No patient was transfused and no postoperative mortality occurred. Morbidity included one acute respiratory distress treated by bronchoscopy and intubation and a readmission for serous abdominal symptomatic collection in the pancreatic bed, which was drained percutaneously. Recovery for both patients went well and they were discharged home. The mean postoperative hospital stay was 7 days. The mean number of lymph nodes harvested was 23 [339].

Laparoscopic surgery

Laparoscopic pancreatic resection of pancreatic cancer is still not universally accepted as an alternative approach to open surgery because of technical difficulties and a lack of consensus regarding the adequacy of this approach for malignancy. Ten patients with pancreatic cancer underwent laparoscopic pancreatic resection, including pancreaticoduodenectomy and distal pancreatectomy in one institution. Eight of the 10 patients recovered without any complications and were discharged on the 10-29th postoperative day. The remaining 2 patients developed pancreatic fistula and were discharged on the 46 and 60th postoperative day, respectively. All lesions were well clear of surgical margins in 6 patients (R0). In the remaining 4 patients, microscopic neoplastic change was found at the surgical margin (R1). Those 4 patients developed tumor recurrence, including liver metastases or peritoneal dissemination, and 3 of the 4 died of the primary disease. Although experience is limited, laparoscopic pancreatic resection of pancreatic cancer can be feasible, safe, and effective in carefully selected patients. However, the benefit of this procedure has yet to be confirmed. Not only adequate experience in pancreatic surgery but also expertise in laparoscopy is mandatory, and careful selection of patients is essential for successful application of this procedure [340].

Surgery in patients with liver cirrhosis

Pancreatic surgery is associated with an increased risk of postoperative complications. It was therefore investigated the impact of an additional liver function disorder on the postoperative outcome using a case-control study of patients with or without liver cirrhosis who underwent pancreatic surgery at our department. Between 1998 and 2008, 1,649 pancreatic resections were performed. Of these, 32 operations were performed in patients who also suffered from liver cirrhosis (30x Child A, 2x Child B). For the case-control study, it was selected another 32 operated patients without cirrhosis who were matched according to age, gender, diagnosis and tumor classification. The following parameters were compared between both groups: operating time, number of transfusions, duration of ICU and hospital stay, incidence of complications, rate of reoperation, mortality. Patients with cirrhosis experienced complications significantly more often (69 vs 44 %), especially major complications (47 vs 22 %) requiring reoperation (34 vs 12 %). These patients also had a prolonged hospital stay (28 vs 24 days) and a significantly longer ICU stay (9 vs 4 days), and required twice as many transfusions. Overall, 3 patients died following surgery, 1 with Child A (3 % of all Child A patients) and 2 with Child B cirrhosis. It was concluded that pancreatic surgery is associated with an increased risk of postoperative complications in patients with liver cirrhosis, and is therefore not recommended in patients with Child B cirrhosis. In Child A cirrhotic patients the mortality is, however, comparable to noncirrhotic patients. Due to the demanding medical efforts that these patients require, they should be treated exclusively in high-volume centers [341].

Management of borderline resectable disease

Resections are attempted in many patients with borderline resectable cancer (ascertained by clinical staging) if the clinician suspects that an R0 resection can be achieved. Optimum preoperative staging can target individuals who should undergo initial chemoradiotherapy rather than surgery. The regimens used for adjuvant and neoadjuvant chemoradiotherapy are those typically administered to patients with borderline resectable disease. In an uncontrolled study of individuals with borderline resectable pancreatic cancer, those receiving neoadjuvant therapy and deemed eligible for pancreatic resection had significantly better survival than those who did not have pancreatectomy. Patients with borderline resectable disease who require vein resections seem to benefit also from adjuvant treatment [213].

Treatment of locally advanced disease

Chemoradiotherapy downstages about 30 percent of patients with locally advanced disease to resectable pancreatic cancer, and these individuals go on to achieve median survival similar to that for those who are initially resectable without any preoperative treatment. Chemotherapy alone is sometimes used for patients too frail to tolerate radiation. Findings of trials in which attempts have been made to ascertain whether chemotherapy alone is preferable to chemoradiation in patients with locally advanced disease have been inconclusive. Although chemoradiotherapy is usually given before systemic chemotherapy, some evidence suggests that scheduling chemotherapy before chemoradiotherapy might be preferable. In patients destined to have rapidly progressive disease, metastases will probably show up during initial chemotherapy and therefore unnecessary local radiotherapy will be avoided [213].

Treatment of metastatic disease

Many combination chemotherapy regimens that show initial promise in phase 2 trials fail to confirm increased survival in phase 3 studies. Meta-analyses have been used to overcome

the disadvantage of small clinical trials. For example, in a meta-analysis of about 3600 patients in phase 3 trials, overall survival was better when gemcitabine was combined with either a platinum-based drug or a fluoropyrimidine, compared with gemcitabine alone, especially for individuals with very good performance status. No standard second-line treatment exists for pancreatic cancer: many patients with advanced disease progress too rapidly to tolerate such regimens. However, second-line fluoropyrimidine-based therapy is sometimes used if gemcitabine has been given as first-line treatment. CT is the standard method for measurement of tumour burden, and clinical trials usually use RECIST (response evaluation criteria in solid tumours) criteria to gauge tumour response. However, CT-based measurements of tumour size do not always quantify treatment response accurately and are usually only established after two cycles of treatment, which is a long time for patients with low survival. Although not sufficiently accurate for diagnosis, serial CA19-9 concentrations predict treatment response or disease relapse. Furthermore, changes in mutant DNA in plasma can be recorded within days of treatment. Moreover, once novel tumour DNA rearrangements are identified in a cancer, their detection in the circulation is feasible. Investigational treatments for advanced pancreatic cancer [213].

Importance of growth in the margins

It has been discussed a greater impact of a positive “transection” margin as compared to the “mobilization” margin following pancreatoduodenectomy for pancreatic ductal adenocarcinoma. It is the recognition of the overwhelming biologic relevance of the systemic disease component of pancreatic cancer, which is important in case we want to make significant strides in improving longterm survival. The shifting of the goalposts in reference to what constitutes a R0 resection may render definitions of oft-debated definitions of “borderline resectable” pancreatic cancer irrelevant because recent reported data is showing a clear disadvantage with R1 resection. It is sobering to consider that most specialists currently treating pancreatic cancer would have retired or completed their surgical careers before a real meaningful breakthrough is made to achieve prolonged survival. It is possibly the manipulation of the milieu in which the cancer cells thrive which needs to be researched further [342].

Cancer of the body and tail

Management of the pancreatic remnant after distal pancreatectomy remains a clinically relevant problem and a significant clinical challenge. It was evaluated the safety and efficacy of duct-to-mucosa pancreaticogastrostomy for preventing pancreatic fistula development after distal pancreatectomy. Twenty-one patients underwent distal pancreatectomy using the duct-to-mucosa pancreaticogastrostomy and the clinical data were collected prospectively. Pancreatic fistula was defined and classified according to the international study group definition. The median surgical time was 236 minutes, with a median intraoperative blood loss of 250 mL. Morbidity was 5 percent and mortality was nil. The postoperative pancreatic fistula rate of clinically relevant grade B or C fistulae was 0 percent, although the biochemical grade A fistula rate was 29 percent. Delayed gastric emptying developed in only 1 patient (5 %). It was concluded that duct-to-mucosa pancreaticogastrostomy may be a safe and effective technique for preventing pancreatic fistula development after distal pancreatectomy when performed by experienced surgeons who are skilled in this technique [343].

The current classification of pancreatic cancer is based only on anatomic location of metastatic lymph nodes (LNs). On the other hand, the number of metastatic LNs has been used in staging of colorectal, esophageal, and gastric cancers. The aim of this study was to assess the prognostic impact of the number or ratio of the metastatic LNs in pancreatic body and tail carcinoma. Eighty-five patients with pancreatic body and tail adenocarcinoma who

underwent pancreatectomy were included. Location, number, ratio of metastatic LNs, and the survival of patients were analyzed. Forty patients with LN metastasis had poor prognosis. The prognoses of patients with 5 or more metastatic LNs were significantly poorer than those with less than 5 metastatic LNs, and patients with a metastatic LN ratio of 0.2 or more had the worst prognosis. Multivariate analysis revealed that 5 or more metastatic LNs and metastatic LN ratio of 0.2 or more were independent prognostic factors for survival. These results indicate that the number and the ratio of metastatic LNs can be used to predict poor patient survival and as a staging strategy [344].

Distal pancreatectomy

The ideal closure technique of the pancreas after distal pancreatectomy is unknown. It was postulated that standardised closure with a stapler device would prevent pancreatic fistula more effectively than would a hand-sewn closure of the remnant. A multicentre, randomised, controlled, parallel group-sequential superiority trial was done in 21 European hospitals. Patients with diseases of the pancreatic body and tail undergoing distal pancreatectomy were eligible and were randomly assigned by central randomisation before operation to either stapler or hand-sewn closure of the pancreatic remnant. Surgical performance was assessed with intraoperative photo documentation. The primary endpoint was the combination of pancreatic fistula and death until postoperative day 7. Patients and outcome assessors were masked to group assignment. Between 2006 and 2009, 450 patients were randomly assigned to treatment groups (221 stapler; 229 hand-sewn closure), of whom 352 patients (177 stapler, 175 hand-sewn closure) were analysed. Pancreatic fistula rate or mortality did not differ between stapler (32 % of 177) and hand-sewn closure (28 % of 175; OR 0.84, 95 % confidence interval 0.53 to 1.33). One patient died within the first 7 days after surgery in the hand-sewn group; no deaths occurred in the stapler group. Serious adverse events did not differ between groups. The authors concluded that stapler closure did not reduce the rate of pancreatic fistula compared with hand-sewn closure for distal pancreatectomy. New strategies, including innovative surgical techniques, need to be identified to reduce this adverse outcome [345].

Open versus laparoscopic pancreatectomy

Laparoscopic left pancreatectomy (LLP) is associated with favorable outcomes compared with open left pancreatectomy (OLP). However, it is unclear if the risk factors associated with operative morbidity differ between these two techniques. A multi-institutional analysis of OLP and LLP performed in 9 academic medical centers was undertaken. LLP cases were defined in an intent-to-treat manner. Perioperative variables were analyzed to identify factors associated with complications and pancreatic fistulae after OLP and LLP. In addition, complication and fistula rates for patients undergoing OLP and LLP were compared in matched cohorts to determine if one approach resulted in superior outcomes over the other. Six hundred and ninety-three left pancreatectomy cases (439 OLP, 254 LLP) were analyzed. OLP and LLP cases were similar with respect to patient age and American Society of Anesthesiologists score. Body mass index (BMI) was higher in patients undergoing LLP. OLP was more often performed for adenocarcinoma and larger tumors, resulted in longer resected specimen lengths, and more commonly involved concomitant splenectomy. Estimated blood loss was higher and operative times were longer during OLP. On multivariate analysis, variables associated with major complications and clinically significant fistulae differed between OLP and LLP. Patients with body mass index ≤ 27 , without adenocarcinoma, and with pancreatic specimen length ≤ 8.5 cm had significantly higher rates of significant fistulae after OLP than after LLP; in contrast, no preoperatively evaluable variables were associated with a higher likelihood of significant fistula after LLP versus OLP. It was concluded that risk factors for complications and pancreatic fistulae after left pancreatectomy differ when open versus laparoscopic techniques are employed. Preoperative characteristics may identify cohorts of patients who will benefit more from LLP,

and no patient cohorts had higher postoperative complication rates after LLP than OLP. These observations suggest that LLP may be the operative procedure of choice for most patients with left-sided pancreatic lesions; but a more definitive prospective and randomized comparison may be warranted [346].

Covering of the stump

Postoperative pancreatic fistula (POPF) remains a significant source of morbidity after distal pancreatectomy (DP). It was described a technique for coverage of the pancreatic stump after DP using a pedicled falciform ligament flap with a low POPF rate. A retrospective review of clinical, radiographic, and pathologic variables of patients undergoing open DP between 2005 and 2009 was performed. After standardized DP, the pancreatic stump was closed using a pedicled falciform ligament flap. Postoperative pancreatic fistula was defined using the International Study Group classification for pancreatic fistula definition. Twenty-three consecutive patients underwent open DP and splenectomy with closure of the pancreatic stump using a pedicled falciform ligament flap. Pancreatic transection and stump closure was performed in a uniform fashion in all patients. Eight patients (35 %) had additional organs resected. Two patients (9 %) developed grade C POPFs, which were successfully managed with percutaneous drain placement. No additional patients developed a POPF or abdominal abscess. The median length of stay was 5 days. There were no perioperative mortalities. It was concluded that use of a pedicled falciform ligament flap for coverage of the pancreatic stump is associated with a low incidence of POPF. Continued investigation of this technique is warranted [347].

Stapler versus hand-sewn closure after distal pancreatectomy

The ideal closure technique of the pancreas after distal pancreatectomy is unknown. It was postulated that standardised closure with a stapler device would prevent pancreatic fistula more effectively than would a hand-sewn closure of the remnant. A multicentre, randomised, controlled, parallel group-sequential superiority trial was done in 21 European hospitals. Patients with diseases of the pancreatic body and tail undergoing distal pancreatectomy were eligible and were randomly assigned by central randomisation before operation to either stapler or hand-sewn closure of the pancreatic remnant. Surgical performance was assessed with intraoperative photo documentation. The primary endpoint was the combination of pancreatic fistula and death until postoperative day 7. Patients and outcome assessors were masked to group assignment. Interim and final analyses were by intention to treat in all patients in whom a left resection was done. Between 2006 and 2009 450 patients were randomly assigned to treatment groups (221 stapler; 229 hand-sewn closure), of whom 352 patients (177 stapler, 175 hand-sewn closure) were analysed. Pancreatic fistula rate or mortality did not differ between stapler (32 %) and hand-sewn closure (28 %; odds ratio 0.84, 95 % confidence interval 0.53 to 1.33). One patient died within the first 7 days after surgery in the hand-sewn group; no deaths occurred in the stapler group. Serious adverse events did not differ between groups. It was concluded that stapler closure did not reduce the rate of pancreatic fistula compared with hand-sewn closure for distal pancreatectomy. New strategies, including innovative surgical techniques, need to be identified to reduce this adverse outcome [348].

Although the past two decades have shown substantial improvements for patients undergoing pancreatic resection, including a large decrease in mortality rates, the management of pancreatic fistula remains vexing. At a minimum, development of a fistula results in added burdens for the patient, as measured by more procedures and increased length of hospital stay. Because many pancreatic resections are for malignancy, a fistula often delays or prevents a patient from receiving potentially beneficial adjuvant therapy. Additionally, fistula is associated with tens of thousands of dollars in increased health-care costs for each patient. The scale of the fistula problem can be exemplified by that 36 percent of patients having a leak [349].

The Appleby operation

Infiltration of the celiac trunk by adenocarcinoma of the pancreatic body has been considered a contraindication for surgical treatment, thus resulting in a very poor prognosis. The concept of distal pancreatectomy with resection of the celiac trunk offers a curative treatment option but implies the risk of relevant hepatic or gastric ischemia. It was described initial experiences in a small series of patients with left celiacopancreatectomy with or without angiographic preconditioning of arterial blood flow to the stomach and the liver. Between 2007 and 2009, six patients underwent simultaneous resection of the celiac trunk for adenocarcinoma of the pancreatic body involving the celiac axis. In four of these cases, angiographic occlusion of the celiac trunk before surgery was performed to enhance collateral flow from the gastroduodenal artery. Radiologic and surgical procedures, findings, and outcome were analyzed retrospectively. Complete tumor removal (R0) succeeded in two patients, whereas four patients underwent R1-tumor resection. After surgery, one of the two patients without angiographic preparation experienced an ischemic stomach perforation 1 week after surgery. The other patient died from severe bleeding from an ischemic gastric ulcer. Of the four patients with celiac trunk embolization, none presented ischemic complications after surgery. Mean survival was 371 days. Thus, in this small series, ischemic complications after celiacopancreatectomy occurred only in those patients who did not receive preoperative celiac trunk embolization [350].

To treat locally advanced cancer of the pancreatic body involving the common hepatic artery and/or celiac axis with perineural invasion in the nerve plexus surrounding these arteries, it has been employed distal pancreatectomy with en bloc celiac axis resection (DP-CAR) without arterial reconstruction. DP-CAR has been performed in patients in whom the gastroduodenal artery and superior mesenteric artery could be preserved. Between 1998 and 2007, 37 patients underwent DP-CAR in one institution. The surgical margins were histologically clear (R0) in 35 (95 %) patients. The postoperative morbidity rate was 59 percent. The primary complications were pancreatic fistula occurring in 19 patients and ischemic gastropathy in 5. Estimated overall 1- and 5-year survival rates were 72 percent and 17 percent, respectively, and the median survival was 21 months. The most common site of recurrence was the liver, where recurrence appeared significantly earlier than in other metastatic sites. DP-CAR, with its potential to achieve complete local control, has been confirmed to be advantageous only in cases that are unlikely to develop hepatic metastasis. In principle, since 2006 patients who have undergone DP-CAR also receive postoperative adjuvant chemotherapy. Patients must achieve feasible general status within 3 months after DP-CAR to be able to start adjuvant chemotherapy [351].

Prognostic factors

TNM

The prognosis of gastrointestinal epithelial malignancies is derived from TNM staging. The nodal status has the most importance. It guides the subsequent adjuvant therapies and gives the oncologist outstanding information about the biology of disease. Recently, a growing number of publications seem to be attributing importance to a ratio of positive to resected lymph nodes as a bad prognostic factor; particularly in gastro-oesophageal carcinomas, colorectal carcinomas and also pancreatic cancer. This particular value predicts the best significance in optimally (nodal) staged carcinomas, with less accurate, but probably equally meaningful information in not adequately resected tumours. Lymph node ratio maintains its value even after neo-adjuvant therapy, a factor known to be able to reduce lymph nodes' retrieval. The lymph node ratio is most accurate when more specialised pathologists in adequate volume cancer centres perform treatment and harvest of the lymph nodes. To date,

no unconventional radiological tool is better able to perform standard armamentarium in correctly defining (preoperatively) patient carriers of massive nodal extension. The accurate definition of nodal staging is crucial for the potential down-staging benefit of neo-adjuvant chemo(radio)therapy on lymph node ratio. In conclusion, lymph node ratio stands out as an independent prognostic factor in adequately (nodal)-staged gastrointestinal epithelial malignancies and could be useful as a stratification factor in future randomised controlled trials [352].

Lymph node ratio

Survival after resection of pancreatic adenocarcinoma is poor. Several prognostic factors such as the status of the resection margin, lymph node status, or tumor grading have been identified. Aim of the study was to evaluate the prognostic significance of the lymph node ratio (LNR) for resected pancreatic ductal adenocarcinoma. Data were collected from 101 patients who had undergone pancreatoduodenectomy for pancreatic ductal adenocarcinoma. Patients were divided into four groups according to the absolute LNR (0, 0-0.199, 0.2-0.399, >0.4). The actuarial 3- and 5-year survival rates were 32 and 17 percent, respectively. The median survival was 19 months. Patients with LNR 0/0-0.199/0.2-0.399/>0.4 survived 40/31/18, and 14 months, respectively. At the multivariate analysis, lymph node status was not found to be a significant prognostic factor; on the contrary LNR >0.2, positive resection margin, and grading were significantly related to survival. It was concluded that LNR is a more powerful predictor of survival than the lymph node status in patients undergoing pancreatoduodenectomy for ductal adenocarcinoma [353].

CA 19-9

The use of chemoradiotherapy (CRT) for localized and unresectable pancreatic cancer has been disputed because of high probability of distant metastasis. Thus, we analyzed the effect of clinical parameters on tumor response, early distant metastasis within 3 months (DM_{3m}), and overall survival to identify an indicator for selecting patients who would benefit from CRT. One study retrospectively analyzed the data from 84 patients with localized and unresectable pancreatic cancer who underwent CRT between 2002 and 2009. Gender, age, tumor size, histological differentiation, N classification, pre- and post-treatment carbohydrate antigen (CA) 19-9 level, and CA 19-9 percent decrease were analyzed to identify risk factors associated with tumor response, DM_{3m}, and overall survival. For all 84 patients, the median survival time was 13 months (range, 2-32 months), objective response (complete response or partial response) to CRT was observed in 28 patients (33 %), and DM_{3m}, occurred in 24 patients (29 %). Multivariate analysis showed that pretreatment CA 19-9 level (≤ 400 vs. >400 U/ml) was significantly associated with tumor response (45 % vs 15 %), DM_{3m}, (20 % vs 42 %), and median overall survival time (15 vs 10 months). For patients with localized and unresectable pancreatic cancer, pretreatment CA 19-9 level could be helpful in predicting tumor response, DM (3m), and overall survival and identifying patients who will benefit from CRT [354].

Postoperative care

Liver ischaemia after pancreatic resection is a rare but potentially serious complication. The aim of one study was to determine the impact of postoperative liver ischaemia after pancreatic resection. All consecutive patients undergoing pancreatic resection between 2007 and 2008 in the Department of Surgery in Heidelberg were identified retrospectively from a prospectively collected database and analyzed with a focus on postoperative hepatic perfusion failure. Laboratory data, computed tomography (CT) findings, symptoms, therapy and outcome were recorded. A total of 762 patients underwent pancreatic resection in the

study period. Seventeen patients (2 percent) with a postoperative increase in liver enzymes underwent contrast-enhanced CT for suspected liver perfusion failure. The types of perfusion failure were hypoperfusion without occlusion of major hepatic vessels (6 patients) and ischaemia with arterial (5) and/or portal vein (6) involvement. The overall mortality rate was 29 percent (5 of 17 patients). Therapy included conservative treatment (7), radiological or surgical revascularization and necrosectomy or resection of necrotic liver tissue (10). Outcome varied from full recovery (4 patients) to moderate systemic complications (6) and severe complications (7) including death. Simultaneous involvement of the portal vein and hepatic artery was always fatal. Postoperative liver perfusion failure is a rare but potentially severe complication following pancreatic surgery requiring immediate recognition and, if necessary, radiological or surgical intervention [355].

Postoperative complications

Rising expenses for complex medical procedures combined with constrained resources represent a major challenge. The severity of postoperative complications reflects surgical outcomes. The magnitude of the cost created by negative outcomes is unclear. Morbidity of 1200 consecutive patients undergoing major surgery from 2005 to 2008 in a tertiary, high-volume center was assessed by a validated, complication score system. Full in-hospital costs were collected for each patient. Statistical analysis was performed using a multivariate linear regression model adjusted for potential confounders. The study population included 393 complex liver/bile duct surgeries, 110 major pancreas operations, 389 colon resections, and 308 Roux-en-Y gastric bypasses. The overall 30-day mortality rate was 1.8 percent, whereas morbidity was 54 percent. Patients with an uneventful course had mean costs per case of USD 27,946 \pm 15,106. Costs increased dramatically with the severity of postoperative complications and reached the mean costs of USD 159,345 \pm 151,191 for grade IV complications. This increase in costs, up to 5 times the cost of a similar operation without complications, was observed for all types of investigated procedures, although the magnitude of the increase varied, with the highest costs in patients undergoing pancreas surgery. The study demonstrates the dramatic impact of postoperative complications on full in-hospital costs per case and that complications are the strongest indicator of costs. Furthermore, the study highlights a relevant savings capacity for major surgical procedures, and supports all efforts to lower negative events in the postoperative course [356].

Although the perioperative mortality of this procedure has markedly decreased during the past 3 decades, it remains significant in relation to other operations of the gastrointestinal tract. With improvements in surgical techniques and critical care, studies from many institutions have reported a substantial decrease in perioperative mortality from 30 percent in the 1970s to as low as 1 percent in the 2000s. Despite this improvement in outcome, a relatively wide range of mortality rates have been reported for this operation. Risk scores may serve various purposes. Pancreatic cancer, which is the most common diagnosis that requires a pancreatectomy, is a disease of the elderly, who may also be experiencing multiple comorbidities. The risks and benefits must be carefully assessed before subjecting these subsets of patients, as well as patients with a higher risk of perioperative mortality, to such major operations. Knowledge of the risk of morbidity and mortality after the procedure that is based on preoperative risk factors in each individual patient is critical in helping the patient to make his or her decision, as well as in satisfying the adequacy of an informed consent. Also, additional therapeutic options, such as salvage procedures, prolonged monitoring in the intensive care unit, or withholding surgery, may be considered in selected patients who may have a high risk of perioperative mortality, provided this information is available at the time of decision making. The net benefits of these therapeutic interventions, in terms of reduction of the risk of perioperative mortality, can also be calculated for individual patients using risk scores. They may also be used in clinical trials to identify certain

risk groups that may be considered for stratification or exclusion from the trial to minimize confounding or for covariate adjustment and subgroup analysis in the trials. In observational studies, risk scores may serve the purpose of propensity scores to minimize selection bias. The predictors of mortality were selected a priori on the basis of clinical usefulness and biological plausibility. To facilitate the use of the model in clinical practice and to ensure building stable models, we chose to restrict the maximum number of predictive parameters to 10 and included only those factors that were readily available preoperatively. Variables included were age, sex, race, histologic diagnosis, type of surgery, preoperative serum albumin and serum creatinine levels, tumor size, and Charlson index. The covariates age, Charlson index, and albumin level were modeled as continuous variables, whereas sex, tumor size, creatinine level, histologic diagnosis, and type of surgery were categorical. Data on tumor size were obtained from surgical pathological evaluation; although it was obtained postoperatively, we included it as a predictor because previous studies have shown a close agreement between tumor size at computed tomography examination and pathological evaluation. The study population (n=1976) consisted of adult patients (≥ 18 years old) admitted to The Johns Hopkins Hospital and who subsequently underwent total pancreatectomy or pancreaticoduodenectomy (classic or pylorus-preserving) from 1998, through 2009. It was excluded patients who underwent distal pancreatectomy because there was only 1 death within 90 days, out of a total of 209 cases, for this procedure (0.48 % mortality). In patients who underwent subsequent procedures, only data from their primary surgery were included. It was restricted the analysis to patients with a histologic diagnosis of benign cystic lesions, periampullary tumors, or neuroendocrine tumors. In a random subset of 70 percent of patients (training cohort), multivariate logistic regression was used to develop a simple integer score, which was then validated in the remaining 30% of patients (validation cohort). The study comprised 1976 patients in a prospectively maintained institutional database who underwent pancreaticoduodenectomy or total pancreatectomy between 1998 and 2009. Most of the patients had multiple comorbidities, with 75 percent (n=1482) of the patient population having a Charlson index of 3 or higher. A randomly selected sample of 70 percent of the total study cohort were a part of the training data set (n=1383), and the remaining 30 percent were a part of the validation data set (n=593). The training and the validation cohorts of patients were seen to be comparable in terms of demographic parameters. In the training cohort, age, male sex, preoperative serum albumin level, tumor size, total pancreatectomy, and a high Charlson index predicted 90-day mortality (area under the curve, 0.78; 95 % confidence interval 0.71 to 0.85), whereas all these factors except Charlson index also predicted 30-day mortality (0.79). On validation, the predicted and observed risks were not significantly different for 30-day (1.4 % vs 1.0 %) and 90-day (3.8 % vs 3.4 %) mortality. Both scores maintained good discrimination (for 30-day mortality, area under the curve, 0.74; 95 % confidence interval 0.54 to 0.95; and for 90-day mortality, 0.73; 95 % confidence interval 0.62 to 0.84). Thus, the risk scores accurately predicted 30- and 90-day mortality after pancreatectomy. They may help identify and counsel high-risk patients, support and calculate net benefits of therapeutic decisions, and control for selection bias in observational studies as propensity scores. For a complete risk assessment, more emphasis should be given to the 90-day mortality rate rather than the 30-day mortality rate. A potential limitation of our study may be that the patient cohort of a single center was used for the development of the model. Because it was a high-volume tertiary referral hospital, the characteristics of the patients may be different from those observed in lower-volume centers. The results of the score should thus be interpreted with caution in centers that may not receive a similar patient population. However, this does not mean that the scores would not perform adequately in other populations, but they may need some simple recalibration of, for example, the risk of mortality. In conclusion, it was have developed and validated a risk score to accurately predict the 30- and 90-day perioperative mortality in patients undergoing pancreatectomy. The risk score will be useful in identifying patients at high risk for perioperative mortality on the basis of simple and easily obtained preoperative risk factors. This information will help in supporting important therapeutic decisions as well as assist in the realization of interventions to improve patient care in high-risk individuals and to calculate

their net benefits. The risk scores may be used for risk stratification in clinical trials and, as propensity scores, may be useful in controlling for selection bias in observational studies. The score will also be beneficial in making individual patients better understand the risks of surgery based on their preoperative characteristics and augment the adequacy of an informed consent [357].

Predictive models

Predictive models to calculate individual surgical mortality are a critical element of "personalized surgery." Risk modeling is particularly suited to technically challenging operations with a narrow therapeutic index, such as radical pancreaticoduodenectomy for pancreatic cancer, and will transform surgery from a "practice" to reproducible performance. Quantifying the perioperative mortality of pancreaticoduodenectomy demystifies a fateful decision for patients with early-stage pancreatic cancer that currently leads 70 percent of patients to choose "none of the above" rather than resection. Second, predictive models identify homogeneous patient populations for enrollment into clinical trials and permit the risk-adjusted analysis of outcomes between centers. Finally, predictive models correct for the effects of patient-related comorbidities on perioperative mortality that would otherwise have an adverse economic effect on surgeons in the era of "pay for performance" regulation [358].

Outcomes for patients undergoing major pancreatic surgery have improved, but a subset of patients that significantly utilize more resources exists. Variables that can lead to an increase in resource utilization in patients undergoing pancreatic surgery were identified. Patients undergoing pancreatic surgery for neoplasms were identified from the NSQIP database (2006-2008). Indices associated with increased resource utilization that we included were operative time (OT), length of stay (LOS), intraoperative RBC transfusion, return to operating room, and occurrence of postoperative complications. Analysis of covariance and multivariable logistic regression were performed. The 4,306 included patients had a median age of 66 years and 50 percent were males. The 30-day morbidity and mortality were 29 percent and 3.2 percent, respectively. Median OT was 362 min and median LOS was 10 days. Malignancy, neoadjuvant radiation, and medical co-morbidities were associated with increased OT. Declining preoperative functional status was the most important predictor of LOS. Age, male gender, hypertension, severe COPD, and higher BMI were significantly associated with postoperative complications. It was concluded that morbidity after pancreatic surgery remains high. Age, obesity, performance status, medical co-morbidities, and neoadjuvant radiation affect outcomes and may lead to increased use of hospital resources [359].

Postoperative bleeding

The aim of this pictorial essay is to illustrate the radiologic patterns, sites of bleeding, and vascular interventional techniques used in the management of postpancreatectomy hemorrhage. It was concluded that hemorrhagic complications occur in fewer than 10 percent of patients after Whipple pancreatoduodenectomy but account for as many as 38 percent of deaths. Bleeding typically occurs from the stump of the gastroduodenal artery, but other sites of bleeding are increasingly recognized [360].

A 31-year-old man underwent a Whipple procedure for a pancreatic neuroendocrine tumor, which consists of a pancreaticoduodenectomy and reconstruction to restore intestinal continuity. Six weeks after the operation, he presented with severe mid-epigastric pain radiating to his back. Imaging studies revealed a large pseudoaneurysm arising from the superior mesenteric artery. Selective superior mesenteric angiography confirmed the presence of the pseudoaneurysm. A 6 mm × 2.5 cm stent graft (Viabhan; W.L. Gore, Flagstaff, Ariz) was deployed across the pseudoaneurysm origin with preservation of the

mesenteric branches. The patient had immediate resolution of symptoms and follow-up imaging showed patency of the stent graft and exclusion of the pseudoaneurysm [361].

Hepatic artery embolization for bleeding

Many collateral pathways to the liver are dissected during hepatobiliary pancreatic surgery and, if the arterial bleeding is massive and a hematoma becomes larger, the adjacent portal vein can be compressed with impairment of the portal venous flow. To evaluate the frequency and severity of ischemic liver injuries after hepatic artery embolization in patients with delayed postoperative arterial hemorrhage after hepatobiliary pancreatic surgery. Eighteen patients undergoing proper or common hepatic artery embolization for delayed postoperative arterial hemorrhage after hepatobiliary pancreatic surgery achieved hemostasis. To evaluate the frequency and severity of ischemic liver injuries, the liver enzyme levels and CT findings before and after hepatic artery embolization were retrospectively compared and the clinical outcomes after hepatic artery embolization were analyzed. Angiographic findings were also analyzed to reveal any association with development of ischemic liver injuries after hepatic artery embolization. Ischemic liver injuries were observed in 15 (83 %) of 18 patients undergoing hepatic artery embolization for postoperative hemorrhage. Injuries included hepatic infarction combined with abscess in one (5 %) patient, hepatic infarction in 12 (67 %) patients, and transient hepatic ischemia or dysfunction in two (11 %). As for the extent of hepatic infarction, lobar infarction developed in two patients and subsegmental infarction in 11. One patient with right hepatic lobar infarction died of hepatic failure 11 days after hepatic artery embolization. In the other 14 patients with ischemic liver injuries, the elevated liver enzymes returned to baseline levels within two weeks. All of the four patients with portal vein stenosis, four patients with no hepatic arterial flow on post-embolization angiogram, and one patient with both had hepatic infarction after hepatic artery embolization. No ischemic liver injuries developed after hepatic artery embolization in three patients with no portal vein stenosis and bilobar hepatic arterial flow via the left hepatic artery aberrantly arising from the left gastric artery or from the common hepatic artery. It was concluded that ischemic liver injuries can develop in most patients undergoing hepatic artery embolization for postoperative arterial hemorrhage after hepatobiliary pancreatic surgery; hepatic infarction appears to be the most frequent type of ischemic liver injury. Hepatic artery embolization for postoperative arterial hemorrhage after hepatobiliary pancreatic surgery may carry a great risk of ischemic liver injury if a patient has portal vein stenosis or no aberrant hepatic artery [362].

It was reported covered stents used for late, postpancreatectomy hemorrhage in the common hepatic artery [363].

Postoperative pancreatic fistula

Postoperative pancreatic fistula (POPF) is a major complication after resective pancreatic surgery. One study aimed to identify histomorphological features of the pancreatic remnant as independent determinants for the development of POPF. Twenty-five patients, 4 percent of 696 resections over a period of 5 years, who developed POPF were matched for age, gender, diagnosis, comorbidities, surgeon and procedure with 25 controls without POPF. Pancreatic duct size and index, fibrosis grade, fat content, edema, and signs of chronic and acute inflammation were measured in frozen sections of the resection margin and were then compared. The POPF rate was 12 and 3 percent after distal pancreatectomy and pancreatoduodenectomy, respectively. The POPF group was characterized by a longer ICU and total postoperative stay, higher rate of reoperations and complications. Their pancreata were softer at palpation (88 vs 56 %). Their pancreatic duct was smaller (2.5 vs 3.2 mm) and their pancreatic fat content higher (16 vs 8 %). High inter- and intralobular fat content, small duct size, low interlobular fibrosis grade and lack of signs of chronic pancreatitis were predictors of POPF development. A score including these parameters identified high-risk

patients with a sensitivity of 92 percent and a specificity of 84 percent. Histomorphological features of the pancreatic remnant play an independent role as risk factors for the development of POPF. A simple histological score based on the frozen sections may already intraoperatively predict the risk of POPF development [364].

Besides the technical aspects, an important feature of high-quality standard surgery is the recognition and treatment of postoperative complications which can, especially in pancreatic surgery, be severe and difficult to handle. One of the most important and potentially life-threatening complications is the occurrence of a postoperative pancreatic fistula which can originate from the pancreatic remnant after distal pancreatectomy or enucleation, as well as from an anastomosis which is usually created as a pancreaticojejunostomy or pancreaticogastrostomy following pancreatic head resections or drainage procedures. Pancreatic fistulae have been described by various authors using non-standardised definitions in the past. In general, the leakage of enzyme-containing fluid from the pancreatic tissue or duct, of any origin and cause, is regarded as a pancreatic fistula. With regard to the postoperative situation, a leakage from the pancreatic stump or the anastomosis can frequently be observed in the very early phase after a resection. Therefore, it is necessary to further clarify the fistula definition with regard to fluid amount, enzyme content and duration of the secretion as well as to correlate these biochemical parameters with the clinical symptoms to evaluate their impact on the patients' condition and to stratify risk levels for possible consequent complications. Up to 2005, twenty-six different definitions of postoperative fistula were used, resulting in a confusing variety of scoring systems with limited clinical value. Furthermore, the reported incidences of fistula of 2-50 percent in different studies were not comparable, making a scientific approach to address this problem difficult. The initial approaches to standardise this definition go back to 2004, when Bassi et al introduced a scoring system including the different features of fourteen fistula definitions based on fluid output measurement and duration of the output. The authors proposed a scoring system in which they summarized four major definitions, which were applied to the studies reviewed for the definition. However, even these four definitions showed significant differently fistula incidences, which led the authors to the conclusion that a consensus conference on this topic was inevitable. Following this consensus, the standardised fistula definition was proposed in 2005 comparable to other complications like delayed gastric emptying and postoperative haemorrhage following this consensus proposal of the International Study Group on Pancreatic Fistula (ISGPF) to achieve a uniform terminology that is suitable for routine clinical use. The ISGPF consensus paper defined a postoperative pancreatic fistula as the existence of any fluid output via an intraoperatively placed or postoperatively inserted drain on or after postoperative day three with an amylase content greater than three times the upper normal serum value. When the diagnosis of a fistula has been established from this simple laboratory finding, it should be further classified regarding the clinical condition, specific therapeutic measures, the duration of treatment, consecutive complications and the outcome of the patient. Consequently, results from different studies have become comparable and the historically reported fistula rates can be evaluated more critically. Furthermore, risk factors for the occurrence and the management have been addressed in several, scientifically valid studies to achieve recommendations for prevention and therapy of this complication. The pancreatic remnant following partial pancreaticoduodenectomy can be handled in different ways with regard to the pancreatic anastomosis. In the 3 available randomised controlled trials, RCTs, no difference in postoperative fistula incidence was found between both techniques, with a common rate of 10-16 percent. Therefore, this topic is still controversial. Concerning tissue texture of the pancreatic remnant, soft tissues and small pancreatic ducts that are usually found in distal bile duct cancers or tumours that are located in the uncinate process without obstructing the pancreatic duct are regarded as critical for a safe anastomosis. This explains the lower fistula rates of 0-5 percent in pancreaticoduodenectomy for chronic pancreatitis compared to other indications. Distal pancreatectomy is performed for all kinds of pancreatic pathologies, including chronic inflammation as well as benign and malignant tumours. The average reported fistula rates are approximately 20-25

percent ranging from 0 to 40 percent. As many of different factors like surgical stump management, spleen preservation, tissue texture or extent of the surgical procedure (e.g. multivisceral resections) can have an impact on fistula development, these issues have been investigated in numerous studies within the last decade. The technique of stump closure after distal pancreatectomy remains the subject of an ongoing debate. All approaches, including fibrin glue, sealants, patches, stapler closure, electrocautery and suture have been tested in numerous studies. The recently completed DISPACT trial included 352 patients that were randomly assigned to stapler or hand-sewn closure of the pancreatic remnant. Both groups showed absolutely equal fistula rates of 30 percent and 36 percent on postoperative day 7 and 30, respectively. The impact of splenic preservation on fistula development is also controversial. When compared to the open approaches in a multicenter study of 200 open versus 142 laparoscopic resections, this rather high fistula rate (26 % laparoscopic vs 32 % open) was confirmed by the same authors without a significant difference between the procedures. Currently, there is no evidence supporting either of the procedures with regard to postoperative fistula development. With regard to the tissue texture of the cut surface after distal pancreatectomy, it is not surprising that the fibrotic tissue in chronic pancreatitis is likely to be less susceptible to fistula development, which explains the significantly lower rates of 3-10 percent. Tumour enucleations of the pancreas represent a type of resection with a rather high reported fistula incidence [365].

The purposes of one study were to validate the value of the International Study Group on Pancreatic Fistula (ISGPF) classification scheme for pancreatic fistula (PF) and to identify predictive factors for clinically significant PF. From 2000 to 2007, 294 consecutive patients underwent pancreaticoduodenectomy in a single medical center. Pancreatic fistula was evaluated by the ISGPF criteria and Johns Hopkins Hospital's definition (JHH). Then, logistic regression analysis was performed to identify predictive factors for PF development. The overall incidence of PF was 19 percent (57/294) according to the ISGPF criteria, and 9 percent (26/294) using the JHH definition. Thirty-one patients with PF classified by the ISGPF were missed by the JHH definition. By logistic regression analysis, it was found that besides the lack of cardiovascular disease and malignant diseases, a single-layer continuous circular invaginated pancreaticojejunostomy was another independent factor for the lowered incidence of PF. It was concluded that the ISGPF classification scheme was accurate for evaluating PF. Single-layer continuous circular invaginated pancreaticojejunostomy may be a promising method that may have been responsible for the lower incidence of PF in this study [366].

Pancreatic fistula rate with or without stenting of the anastomosis

Pancreatic fistula (PF) is a leading cause of morbidity and mortality after pancreaticoduodenectomy (PD). The aim of one multicenter prospective randomized trial was to compare the results of PD with an external drainage stent versus no stent. Between 2006 and 2009, 158 patients who underwent PD were randomized intraoperatively to either receive an external stent inserted across the anastomosis to drain the pancreatic duct (n=77) or no stent (n=81). The criteria of inclusion were soft pancreas and a diameter of Wirsung <3 mm. The primary study end point was PF rate defined as amylase-rich fluid (amylase concentration >3 times the upper limit of normal serum amylase level) collected from the peripancreatic drains after postoperative day 3. CT scan was routinely done on day 7. The two groups were comparable concerning demographic data, underlying pathologies, presenting symptoms, presence of comorbid illness, and proportion of patients with preoperative biliary drainage. Mortality, morbidity, and PF rates were 3.8 percent, 52 percent, and 34 percent, respectively. Stented group had a significantly lower overall PF (26 % vs 42 %), morbidity (42 % vs 62 %), and delayed gastric emptying (8 % vs 27 %) rates compared with nonstented group. Radiologic or surgical intervention for PF was required in 9 patients in the stented group and 12 patients in the nonstented group. There were no significant

differences in mortality rate (3.7 % vs 3.9 %) and in hospital stay (22 days vs 26 days). The authors concluded that external drainage of pancreatic duct with a stent reduced pancreatic fistula and overall morbidity rates after PD in high risk patients (soft pancreatic texture and a nondilated pancreatic duct) [367].

Intraabdominal drains are commonly used in most centres after pancreatic resections. There is no evidence that persisting drainage of postoperative wound fluid has a positive effect in avoiding fistulae. The mechanisms, such as mechanical irritation of the anastomosis, are not fully clear. The placement of duct stents to protect the anastomosis from pancreatic fluid is established and practised by several centres around the world. However, the principle of an internal drainage, although this might be reasonable from the mechanistic point of view to achieve a diversion of the pancreatic secretion from the suture site, must be discussed, as the drain may also cause problems via irritation of the duct and the suture lines as well as obstruction or migration. In the available studies, this outcome shows a great deal of variability. Two larger studies demonstrated a beneficial effect of anastomotic stenting, including a study by Roder et al that included 85 patients (44 stent, 41 no stent, fistula rates 7 % vs 29 %, respectively) and a randomised trial by Poon et al among 120 patients, which showed that the externally-stented group had a significantly lower pancreatic fistula rate compared to the non-stented group (7% vs 20 %, respectively). On the other hand, a non-randomised study by Imaizumi et al with 168 patients showed no significant difference in fistula rates using stented (internal or external) versus non-stented methods (6 % vs 7 %, respectively). The largest randomized study, published in 2006 by Winter et al included 234 patients who underwent pancreatico-duodenectomy with stent (n=115) or without stent (n=119) placement into the pancreatic duct. The collective was additionally stratified according to the tissue texture (soft vs hard). With an overall fistula rate of 8 percent (no stent) versus 11 percent (stent), this study could not show any benefit in either the hard or soft pancreatic remnants (fistula rate 11 % vs 21 %, respectively). Based on the current evidence, it remains unclear as to whether stenting of the pancreatic duct can reduce the fistula rate after pancreatico-duodenectomy, making a general recommendation on this topic impossible [365].

Prevention

The use of octreotide and its analogues to prevent postoperative fistula is an approach which has been used since the 1990s. Despite twenty years of clinical use and performance in numerous studies, a recent Cochrane meta-analysis concluded that evidence is still lacking to give clear recommendations or guidelines. While early RCTs favoured the use of octreotide and showed a 50 percent reduction of fistula rates these findings were not confirmed in later trials. From these results, it was consequently concluded that routine use of octreotide was not favourable, but should be used in a risk-dependant manner in presumed "critical" anastomoses due to soft pancreatic tissue texture. The latest Cochrane review supported this, in part. Although the overall fistula rates have been reduced, somatostatin analogues failed to reduce the incidence of clinically relevant (type B/C) fistulae or re-operation rates and mortality. In patients undergoing surgery for malignancies, overall hospital stay was shortened by somatostatin application, which led the authors to conclude that these patients might benefit from routine somatostatin use. For distal pancreatectomies and drainage operations, no recommendation was possible due to a lack of valid studies [365].

Fistula-associated complications

Once a pancreatic fistula is evident in the postoperative course, prevention of consecutive complications is essential. Commonly-observed complications are mainly caused by undrained pancreatic fluid and superinfection of fluid collections. As pancreatic fluid is an enzymatically active and aggressive substance, erosional complications can affect the surrounding tissue, namely the intestinal, bile duct or vessel walls. This can lead to a leakage of increasing size at the pancreatic anastomosis itself, to a secondary leakage of the bile

duct anastomosis or the gastro-enterostomy, as well as to additional anastomoses, e.g. in multivisceral resection. However, the most severe and dangerous complication is an acute bleeding episode, which usually arises from enzymatically- damaged vascular sutures (e.g. the stump of the gastroduodenal or splenic artery, or portal vein anastomosis). Interventional or surgical management of these bleeding episodes can be an interdisciplinary challenge. The occurrence of infected pancreatic fluid collection due to a fistula is also a critical situation for an ongoing abdominal sepsis that can quickly lead to generalised systemic organ failure. Sufficient drainage of the fluid and wide antibiotic therapy are as important as supportive ICU therapy in these patients. An interesting and important aspect of fistula-associated complications is the economic impact, which accompanies the often long-lasting treatment. Especially, the longer duration of hospital stay is an important factor that increases treatment costs [365].

Management of pancreatic fistula

The management of postoperative fistula remains a therapeutic challenge and underlines the importance of specific surgical, radiological and, if necessary, anaesthesiological ICU care knowledge. As every fistula is a potentially life-threatening complication for the patient, early detection and careful management is of the highest priority to avoid consequent complications. Depending on the clinical symptomology and the condition of the patient, fistula management ranges from persisting drainage without any further measures, up to revision surgery with remnant pancreatectomy. A clinically uncomplicated type A fistula can usually be managed by drainage alone, which means the intraoperatively placed drains which are still in situ are kept as long as necessary, usually between 2 and 4 weeks, to enable a spontaneous closure of the fistula. Besides clinical control of the symptoms, amylase and lipase content should be regularly controlled as well as the 24 h fistula output volume and inflammatory parameters including leucocyte count and C-reactive protein, to avoid unrecognised fluid collections causing infectious complications despite persisting drainage. If drains have already been removed, fistulae usually display clinical symptoms as described above as they can cause a collection of undrained fluid. These type B fistulae are generally recognised by CT scan and interventional drain placement. Afterwards, continuous drainage should be maintained and antibiotic treatment is often mandatory to avoid ongoing abdominal infection. Under this regimen, fistulae often resolve within a 2-4 week period, similar to those drained primarily. In contrast, type C fistulae require more aggressive therapies. The most critical situation is the development of erosional bleeding that can arise from the splenic artery and vein or other visceral vessels due to enzymatic digestion combined with bacterial contamination. Bleeding episodes are often preceded by sentinel bleeding, but can also occur acutely without any warning event.⁶ In the case of bleeding, the patient must be referred to intensive care therapy, stabilised if required by resuscitation and must undergo immediate diagnostics to localise the bleeding site. The common algorithm is a contrast-enhanced CT scan to visualise the site of bleeding and associated collections, followed by arterial angiography of the visceral segment. Angiography should not only aim at the localisation, but also achieve bleeding control by interventional treatment including stent placement or coiling of the erosively-damaged vessel. An operative intervention has to be considered when bleeding control cannot be achieved interventionally or when further complications seem to be likely. In these cases, operative bleeding control by vessel ligation can be mandatory and a remnant pancreatectomy has to be taken into account to control the fistula as the causative complication. Especially after partial pancreatico-duodenectomy, remnant pancreatectomy can be beneficial, as this procedure is practicable and can be combined with an extensive lavage of the abdominal cavity to achieve best conditions for the usually critically ill patient. An emergency resection of the pancreatic head to control complicated fistulae after distal pancreatectomy is a very rare event, as these fistulae can usually be managed without surgical revision and the procedure is associated with a considerable morbidity and mortality that make it an unfavourable approach that is certainly limited to very special indications. In contrast to application of somatostatin and its analogues

in the prevention of postoperative fistulae, which has been investigated in various high-quality reviews, therapeutic use of is not considered as an evidence-based approach yet [365].

ISGPF grading system of postoperative pancreatic fistulae (POPF) [365]

	Grade A	Grade B	Grade C
Clinical condition	Well	Often well	Ill appearing/bad
Specific treatment	No	Yes/No	Yes
Ultrasound/CT scan	Negative	Neg/Pos	Positive
Persistent drainage (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
POPF related death	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

Lymph node metastases

A review on the unique patterns of metastases by common and rare types of cancer addresses regional lymphatic metastases but also demonstrates general principles by consideration of vital organ metastases. These general features of successfully treated metastases are relationships to basic biological behavior as illustrated by disease-free interval, organ-specific behavior, oligo-metastatic presentation, genetic control of the metastatic pattern, careful selection of patients for surgical resection, and the necessity of complete resection of the few patients eligible for long-term survival after resection of vital organ metastasis. Lymph node metastases, while illustrating these general features, are not related to overall survival because lymph node metastases themselves do not destroy a vital organ function, and therefore have no causal relationship to overall survival. When a cancer cell spreads to a regional lymph node, does it also simultaneously spread to the systemic site or sites? Alternatively, does the cancer spread to the regional lymph node first and then it subsequently spreads to the distant site(s) after an incubation period of growth in the lymph node? Of course, if the cancer is in its incubation stage in the lymph node, then removal of the lymph node in the majority of cases with cancer cells may be curative. The data from the sentinel lymph node era, particularly in melanoma and breast cancer, is consistent with the spectrum theory of cancer progression to the sentinel lymph node in the majority of cases prior to distant metastasis. Perhaps, different subsets of cancer may be better defined with relevant biomarkers so that mechanisms of metastasis can be more accurately defined on a molecular and genomic level [368].

Prognosis of lymph node metastasis

Lymph node status is one of the most important predictors of survival in pancreatic ductal adenocarcinoma. Surgically resected pancreatic adenocarcinoma is often locally invasive and may invade directly into peripancreatic lymph nodes. The significance of direct invasion into lymph nodes in the absence of true lymphatic metastases is unclear. The purpose of this study was to retrospectively compare clinical outcome in patients with pancreatic ductal adenocarcinoma with direct invasion into peripancreatic lymph nodes with patients with node-negative adenocarcinomas and patients with true lymphatic lymph node metastasis. A total of 380 patients with invasive pancreatic ductal adenocarcinoma classified as pT3, were evaluated: ductal adenocarcinoma with true lymphatic metastasis to regional lymph nodes (248 cases), ductal adenocarcinoma without lymph node involvement (97 cases), and ductal adenocarcinoma with regional lymph nodes involved only by direct invasion from the main tumor mass (35 cases). Isolated lymph node involvement by direct invasion occurred in 35 of

380 (9 %) patients. Overall survival for patients with direct invasion of lymph nodes (median survival, 21 mo; 5-year overall survival, 36 %) was not statistically different from patients with node-negative adenocarcinomas (median survival, 30 mo; 5-year overall survival, 31 %). Patients with node-negative adenocarcinomas had an improved survival compared with patients with lymph node involvement by true lymphatic metastasis (median survival, 15 mo; 5-year overall survival, 8 %) regardless of the number of lymph nodes involved by adenocarcinoma. There was a trend toward decreased overall survival for patients with 1 or 2 lymph nodes involved by true lymphatic metastasis compared with patients with direct invasion of tumor into lymph nodes. However, this did not reach statistical significance. Our results indicate that patients with isolated direct lymph node invasion have a comparable overall survival with patients with node-negative adenocarcinomas as opposed to true lymphatic lymph node metastasis [369].

Postoperative exocrine insufficiency

Most studies have looked at pancreatic exocrine function following surgery for chronic pancreatitis. These studies have confirmed high levels of pancreatic exocrine insufficiency (PEI) postoperatively, which required enzyme supplementation. Studies which have assessed pancreatic exocrine function following surgery for pancreatic tumours have focussed on the type of pancreatic anastomosis, postoperative imaging, and risk factors. The follow-up times for these studies have been variable and the majority has not performed QoL analyses. Additionally, most of these studies have used indirect methods of estimating pancreatic exocrine function such as N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test, ¹³C-labelled mixed triglyceride test, faecal elastase test, and secretin-stimulated dynamic magnetic resonance pancreatography, without comparison to the criterion standard of stool fat collection and analysis. Following resection and reconstruction it is not usually possible and may be hazardous to perform the secretin-caerulein intubation test. Direct measurement of faecal fat (and the coefficient of fat absorption, CFA) is accurate and sensitive but is cumbersome, time-consuming and requires specialised facilities. Faecal elastase-1 (FE-1), although an indirect test, is becoming more commonly used clinically to test for PEI. FE-1 has the advantages of ease of use and is relatively sensitive and specific. It is clearly not as robust as direct measures as it only measures enzyme secretion, whereas fat absorption also requires normal luminal pH and mixing of enzymes and food, both of which may be disturbed by surgery; additionally, postoperative diarrhoea for other reasons (e.g. bowel denervation) may give false-low readings of FE-1. The most frequently described change of pancreatic exocrine function after resectional surgery is steatorrhea, which is defined as a stool fat content of >7 g/day (when diet contains 100 g of fat) with associated symptoms of abdominal pain, flatus and weight loss. Malabsorption of fat occurs when pancreatic lipase and trypsin falls to below 5-10 percent of normal production, although the mechanisms resulting in intraluminal pancreatic enzyme deficiency are multiple and overlapping. One study examined the coefficient of fat absorption (CFA), symptoms, quality of life (QoL) and the accuracy of faecal elastase-1 (FE-1) measurement to predict PEI. Coefficient of fat absorption was measured at four assessments during the study (at 6 weeks following surgery, then 3, 6 and 12 months). Stool was collected on 3 consecutive days (72 h). The patients followed a diet regimen for the 24 h prior to stool fat collection and the 3 days during. The total fat intake per 24 h was 70 or 100 g depending on patient compliance and weight. Stool weight (g/day) was calculated from the net weight of the 72-hour stool collected divided by 3. A CFA of >93% was taken as normal pancreatic exocrine function. Forty patients were analysed following resection for pancreatic malignancy. Resection of the head of the pancreas was undertaken in a standard manner. Lymph nodes 8 and 16 were routinely sampled. Reconstruction in this series was achieved by: an end-to-side pancreatico-jejunostomy (Cattell-Warren method using an internal pancreatic stent), an end-to-side hepatico-jejunostomy and an antecolic pyloro-jejunostomy. Kausch-Whipple partial

pancreato-duodenectomy differed only in gastric antrum resection with an antecolic gastro-jejunostomy. Left pancreatectomies were performed by mobilising the pancreas along its superior and inferior borders. The splenic artery and vein were ligated and divided prior to excision of gland. The spleen was preserved in the case of simple excision with the pancreatic duct either sutured or stapled. The primary endpoint was PEI diagnosis defined by CFA <93 percent; secondary endpoints were PEI diagnosis using FE-1 <200 µg/g, body mass index (BMI), and symptom and QoL analysis. Interventions were 3-day stool collection, EORTC QLQ-C30 (version 1) questionnaire and patient's diary, at 6 weeks and 3, 6 and 12 months after surgery. CFA <93 percent was present in 67 percent of patients at 6 weeks and in 55 percent at 12 months. PEI using FE-1 was present in 77 and 83 percent of patients, respectively. No significant changes between time-points were observed. Sensitivity, specificity, PPV, NPV and accuracy for FE-1 in detecting CFA <93 percent were 91, 35, 70, 71 and 70 percent, respectively. CFA and FE-1 levels were uncorrelated. The mean scores for QoL and main attributes driving was identified comprising a small subset of the variables that could be viewed as drivers of QoL which were physical function, role function, social function and appetite. QoL remained static up to 3 months after surgery but was associated with an initial deterioration of physical function and role function, which gradually recovered over time and normalized by 6 months. QoL then significantly improved at 6-12 months mirrored by and driven by an increase in social function and appetite from 3 months after surgery. On the whole, patients with PEI scored lower on QoL and the functional scores and higher on the symptom attributes indicating poorer QoL in those patients with PEI. The overall differences, however, were not significant with the single exception of insomnia. There was no association between type of surgery or diagnosis and PEI, symptoms or QoL. Importantly, however, BMI and symptoms were unaffected by PEI, which suggests a subclinical presentation; such patients had attributes indicating poorer QoL (notably insomnia). The study has thus shown that the majority of patients had PEI by 6 weeks postoperatively and was sustained at 12 months. Direct testing of faeces for fat content is not commonly used clinically as it is unpleasant and requires specialized facilities, hence the popularity of indirect methods. There is, however, considerable concern of the overall accuracy of FE-1 in diagnosing PEI, as it is known that it correlates poorly to CFA. The poor overall accuracy of FE-1 is centred on the poor specificity in detecting PEI. At a cut-off of 200 µg/g, it is 35 percent, rising to 44 percent if dropped to 128 µg/g. Even allowing for further optimisation by increasing the CFA threshold for diagnosis to <94 percent, the specificity of FE-1 to diagnose PEI was only 50 percent. This is simply insufficient to operate as a diagnostic test. Interestingly, patient symptoms and BMI remained static though the course of the study. The longer-term survival, however, was reduced in patients with cachexia. The main drivers for QoL were physical, role and social function and improvement of appetite. Although QoL scores were higher in the non-PEI group when compared to the PEI group when the means of the attributes were mapped, the absolute difference was not significant. Of considerable interest, however, was the finding of a hugely significant association between insomnia and PEI [370].

The aim of one study was to investigate whether perioperative morphologic characteristics are predictive of exocrine pancreatic function after pylorus-preserving pancreato-duodenectomy (PPPD) with pancreaticogastrostomy. A ¹³C-labeled mixed triglyceride breath test was performed in 52 patients after PPPD to assess postoperative exocrine pancreatic function. A value of percent ¹³CO₂ cumulative dose at 7 h (%CD-7 h) of less than 5% was considered diagnostic of exocrine pancreatic insufficiency. Pre- and postoperative pancreatic parenchymal thicknesses were calculated using computed tomography (CT) scans, and compared by means of receiver operating characteristic (ROC) analysis. Thirty-four (65 %) of 52 patients were found to have exocrine pancreatic insufficiency based on the breath test. With ROC analysis for identification of exocrine pancreatic insufficiency, the areas under the ROC curve for the postoperative pancreatic parenchymal thickness were higher than those for the preoperative pancreatic parenchymal thickness (0.90 and 0.70, respectively). When the cut-off value of the postoperative pancreatic parenchymal thickness was set at 13 mm,

the sensitivity and specificity for identifying exocrine pancreatic insufficiency were 88 percent and 89 percent, respectively. It was concluded that reduced postoperative pancreatic parenchymal thickness is a reliable indicator of exocrine pancreatic insufficiency after PPPD [371].

Percutaneous transhepatic stent in the management of portal venous stenosis

The purpose of one study was to evaluate the efficacy and safety of stent placement in the management of portal venous stenosis after curative surgery for pancreatic and biliary neoplasms. From 1995 to 2007, percutaneous transhepatic portal venous stent placement was attempted in 19 patients with postoperative portal venous stenosis. Portal venous stenosis was a complication of surgery in 11 patients and caused by tumor recurrence in eight patients. The clinical manifestations were ascites, hematochezia, melena, esophageal varices, and abnormal liver function. Stents were placed in the stenotic or occluded lesions after percutaneous transhepatic portography. Technical and clinical success, stent patency, and complications were evaluated. Stent placement was successful in 18 patients (technical success rate, 95 %). Clinical manifestations improved in 16 patients (clinical success rate, 84 %). The mean patency period among the 18 patients with technical success was 21 ± 23 months. The mean patency period of the benign stenosis group (30 ± 26 months) was longer than that of the tumor recurrence group (7 ± 8 months), and the difference was statistically significant. There were two cases of a minor complication (transient fever) and three cases of major complications (septicemia, liver abscess, and acute portal venous thrombosis). Percutaneous transhepatic stent placement can be safe and effective in relieving portal venous stenosis after curative surgery for pancreatic and biliary neoplasms. Patients with benign stenosis had more favorable results than did those with tumor recurrence [372].

Venous thromboembolism

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in patients with cancer. The risk of VTE varies over the natural history of cancer, with the highest risk occurring during hospitalization and after disease recurrence. Patient and disease characteristics are associated with further increased risk of VTE in this setting. Specific factors include cancer type (e.g. pancreatic cancer, brain cancer, lymphoma) and the presence of metastatic disease at the time of diagnosis. VTE is a significant predictor of increased mortality during the first year among all types and stages of cancer, with metastatic disease reported to be the strongest predictor of mortality. VTE is also associated with early death in ambulatory patients with cancer. These data highlight the need for close monitoring, prompt treatment, and appropriate preventive strategies for VTE in patients with cancer. The American Society of Clinical Oncology and the National Comprehensive Cancer Network have issued guidelines regarding the prophylaxis and treatment of patients with cancer. One review summarized the impact of VTE on patients with cancer, the effects of VTE on clinical outcomes, the importance of thromboprophylaxis in this population, relevant ongoing clinical trials examining the prevention of VTE, and new pharmacologic treatment options [373].

Pulmonary embolism

Incidence of pulmonary embolism (PE) for different cancer types in oncology outpatients is unknown. The purposes of the current study are to determine the incidence of PE in oncology outpatients and to investigate whether the incidence for PE is higher in certain cancers. A cohort of oncology outpatients who had imaging studies at a tertiary outpatient cancer institute, from 2004 through 2009 was identified using research patient data registry.

Radiology reports were reviewed to identify patients who developed PE. Incidences of PE in the total population and in each of 16 predefined cancer groups were calculated. Risk of PE for each cancer was compared using Fisher exact test. A total of 13,783 patients was identified, of which 395 (2.87 %; 95% confidence interval 2.59 to 3.16) developed PE. The incidence of PE was highest in the central nervous system (CNS), hepatobiliary, pancreatic (5.81 %; 95 % confidence interval 3.59 to 8.84), and upper gastrointestinal. The risk of PE was significantly higher for CNS, pancreatic (OR 2.15), upper gastrointestinal, and lung/pleural malignancies. There was significantly lower risk of PE for hematologic and breast malignancies. Thus, the incidence of PE in oncology outpatients in a tertiary cancer center during a 6-year period was 2.9 percent. CNS, pancreatic, upper gastrointestinal, and lung/pleural malignancies had a significantly higher risk for PE than other malignancies, whereas hematologic and breast malignancies had a significantly lower risk [374].

Coeliac plexus block

Pancreatic cancer causes severe pain in 50 to 70 percent of patients and is often difficult to treat. Celiac plexus block (CPB) is thought to be a safe and effective technique for reducing the severity of pain. To determine the efficacy and safety of celiac plexus neurolysis in reducing pancreatic cancer pain, and to identify adverse effects and differences in efficacy between the different techniques it was searched Cochrane CENTRAL, MEDLINE, GATEWAY and EMBASE from 1990 to December 2010. It was searched randomised controlled trials (RCTs) of CPB by the percutaneous approach or endoscopic ultrasonography (EUS)-guided neurolysis in adults with pancreatic cancer at any stage, with a minimum of four weeks follow-up. It was recorded details of study design, participants, disease, setting, outcome assessors, pain intensity (visual analogue scale (VAS)) and methods of calculation. The search identified 102 potentially eligible studies. Judged from the information in the title and abstract six of these concerning the percutaneous block, involving 358 participants, fulfilled the inclusion criteria and were included in the review. All were RCTs in which the participants were followed for at least four weeks. It was excluded studies published only as abstracts. It was identified one RCT comparing EUS-guided or computed tomography (CT) -guided CPB but its aim was to assess efficacy in controlling chronic abdominal pain associated with chronic pancreatitis rather than pancreatic cancer, so it was excluded. For pain (VAS) at four weeks the mean difference was -0.42 in favour of CPB (95 % confidence interval -0.70 to - 0.13). At eight weeks the mean difference was -0.44 (95 % confidence interval -0.89 to - 0.01, random-effects model). Opioid consumption was significantly lower in the CPB group than the control group. The authors concluded that although statistical evidence is minimal for the superiority of pain relief over analgesic therapy, the fact that CPB causes fewer adverse effects than opioids is important for patients. Further studies and RCTs are recommended to demonstrate the potential efficacy of a less invasive technique under EUS guidance [375].

EUS-guided

Abdominal pain in patients with pancreatic cancer is a common symptom that is often difficult to manage. Opioids are frequently used in an attempt to mitigate pain; however, side effects may develop. Celiac plexus neurolysis (CPN) affords effective pain control in patients with pancreatic cancer and is not associated with opioid side effects. Endoscopic ultrasound (EUS)-guided CPN has demonstrated safety and efficacy due to real-time imaging and anterior access to the celiac plexus from the posterior gastric wall, thereby avoiding complications related to the puncture of spinal nerves, arteries and the diaphragm, and is now practiced widely. Furthermore, two new techniques of EUS-guided neurolysis for abdominal pain management in pancreatic cancer patients have recently been developed. The first technique is EUS-guided celiac ganglia neurolysis (EUS-CGN) in which EUS

facilitates CGN by enabling direct injection into the individual celiac ganglion, and the second technique is EUS-guided broad plexus neurolysis (EUS-BPN) which extends over the superior mesenteric artery. One review provided evidence for the efficacy of EUS-CPN. Particular attention is paid to the two new techniques of EUS-guided neurolysis, EUS-CGN and EUS-BPN [376].

Other palliative measures

Erythropoietin

Erythropoietin (EPO) is a glycoprotein that is mainly produced in the adult kidney, and it was initially highlighted for its action on the hematopoietic system. Moreover, EPO is also expressed in several non-hematopoietic tissues, where it plays a role in the protection from apoptosis and inflammation due to hypoxia, toxicity or injury. These protective effects are mainly known and studied in cardioprotection and neuroprotection but are also reported in retina degeneration, auditory injury and pancreatic-related diseases. The tissue protective effect of EPO is mainly mediated through the interaction with the heterodimeric receptor EPOR/betacR. Human recombinant EPO (HuREPO), which has been developed to treat anemia, is not adequate for tissue protection. The low affinity of the alternative receptor for EPO involves the injection of excessive concentration of erythropoiesis-stimulating agents (ESAs), implicating side effects due to the cross-talk with hematopoietic activity. For these reasons, EPO derivatives with less affinity for the EPO homodimeric receptor are under development. In this review, we provide an overview of the erythroid and non-erythroid functions of EPO by detailing the molecular mechanisms activated by the binding of EPO to its receptors in different tissues [377].

Supportive care

Findings show that palliative care can help patients even as they are undergoing treatment for advanced disease. Supportive care begins with provision of support and information from the time of diagnosis and the appropriate amount of hope for the patient's stage of disease. Pain management is an important component of treatment. Identification of the cause of pain can guide effective therapy. Pain from coeliac plexus infiltration can be treated effectively with endoscopic ultrasound or CT-guided ablation of the plexus. Radiation can relieve pain from locally advanced disease. Most patients with pancreatic-head cancers will develop obstructive jaundice and benefit from biliary stenting. Metal stents remain patent for longer than do plastic ones. About 20 percent of individuals develop gastric-outlet obstruction and benefit from duodenal wall stents or PEG (percutaneous endoscopic gastrostomy) placement for decompression. Owing to the effectiveness of endoscopic wall stents, surgical management of obstructive jaundice and gastric outlet obstruction is usually not necessary, although it could provide better palliation for individuals with long life expectancy. Since patients with pancreatic cancer frequently develop venous thromboembolism, prophylaxis is recommended. Because of the nature of the hypercoagulable state, findings of several randomised trials indicate that lowmolecular-weight heparin provides better prophylaxis than warfarin. Pancreatic enzyme therapy is sometimes needed because of pancreatic-duct blockage or sparse pancreatic-gland tissue [213].

Prognosis of survival

Accurate prognosis facilitates decision-making and counselling in incurable cancer. However, predictions of survival are frequently inaccurate and survival is consistently overestimated. The prognostic skills of surgeons are sparsely documented, and the present study was undertaken to assess their prognostic accuracy for patients with advanced abdominal malignancy. Clinical predictions of survival were made by three consultant surgeons

independently in consecutive patients with incurable abdominal cancer. Survival was predicted in intervals ranging from <1 week to 18-24 months. Prognoses were considered accurate when actual survival fell within the expected range. Performance status was classified according to the Eastern Cooperative Oncology Group (ECOG). 243 assessments were made in 178 patients. Prognoses were accurate in 27 percent, over-optimistic in 42 percent and over-pessimistic in 31 percent. Accuracy was inversely related to length of actual survival and did not differ between surgeons. The proportion of over-optimistic prognoses differed significantly between surgeons. Prognostic accuracy was 44 percent in gastric cancer patients, 29 percent in pancreatic cancer patients and 22 percent in colorectal cancer patients. ECOG performance status correlated well with survival. Surgeons' accuracy in determining prognosis is poor. There are considerable individual differences between surgeons, and accuracy is reduced in cases with prolonged life expectancy [378].

Quality of life

One study assessed whether pretreatment quality-of-life (QoL) scores could predict the presence of pancreatic malignancy and survival. Patients with pancreatic lesions completed the SF-36, containing 8 domains: physical functioning, role-physical, role-emotional, bodily pain, vitality, mental health, social functioning, and general health. Data obtained included age, sex, resectability, additional antineoplastic therapy, stage, pathology, and survival. Patients were categorized by pathology (benign vs malignant), stage (local, regional, or distant), resectability (resected vs not), survival (<1 vs >1 year), and their pretreatment QoL scores. Of the 323 patients assessed, 210 had malignancies. In 6 of the 8 domains, patients with malignancies had lower median QoL scores compared with patients with benign lesions. Of the patients with malignancies, patients surviving at 1 year or less had lower pretreatment scores in all domains. Stage, resection, adjuvant therapy, and vitality score were independent predictors of survival. It was concluded that patients with pancreatic malignancies had lower QoL scores than patients with benign pancreatic disease. Patients with malignancies surviving at 1 year or less had lower scores, even after controlling for stage. This suggests that pretreatment QoL scores are associated with pancreatic malignancy and survival [556].

Terminal care

The authors' goal was to characterize hospice enrollment and aggressiveness of care for pancreatic cancer patients at the end of life. Surveillance, Epidemiology, and End Results and linked Medicare claims data (1992-2006) were used to identify patients with pancreatic cancer who had died (n=22,818). The authors evaluated hospice use, hospice enrollment ≥ 4 weeks before death, and aggressiveness of care as measured by receipt of chemotherapy, acute care hospitalization, and intensive care unit (ICU) admission in the last month of life. Overall, 57 percent of patients enrolled in hospice, and 36 percent of hospice users enrolled for 4 weeks or more. Hospice use increased from 36 percent in 1992-1994 to 67 percent in 2004-2006. Admission to the ICU and receipt of chemotherapy in the last month of life increased from 16 percent to 20 percent and from 8 percent to 16 percent, respectively. Among patients with locoregional disease, those who underwent resection were less likely to enroll in hospice before death and much less likely to enroll early. They were also more likely to receive chemotherapy (14 % vs 9 %), be admitted to an acute care hospital (61 % vs 53 %), and be admitted to an ICU (27 % vs 15 %) in the last month of life. It was concluded that although hospice use increased over time, there was a simultaneous decrease in early enrollment and increase in aggressive care at the end of life for patients with pancreatic cancer [555].

Medical treatment of pancreatic cancer

Neoadjuvant therapy

Although no data are available from randomised controlled trials to support neoadjuvant over adjuvant therapy, findings of a meta-analysis suggest the proportion of patients who can have resection is similar, whether or not neoadjuvant treatment is given. Neoadjuvant therapy does yield partial responses and has the potential to downstage patients with borderline resectable disease, and it is usually recommended in this setting. Neoadjuvant treatment can detect patients whose disease progresses rapidly and, therefore, it could help to select those who might not benefit from surgical resection. Another potential advantage of neoadjuvant therapy is that postoperative complications do not delay or preclude administration of adjuvant treatment. Conversely, tumour response rates to current neoadjuvant therapies are not high, and delaying surgical resection could also allow disease progression. For this reason, patients undergoing neoadjuvant therapy should be restaged before surgical resection. The optimum neoadjuvant regimen is not yet known, although combination chemotherapy schedules are usually given. Since no advantage has been recorded of neoadjuvant treatment over adjuvant therapy for patients with clearly resectable disease, and strong evidence exists that adjuvant therapy increases survival, most centres use adjuvant treatment, reserving neoadjuvant therapy for patients with borderline resectable disease [213].

To improve the likelihood of achieving a margin-free resection, neoadjuvant induction chemotherapy with GTX (gemcitabine, docetaxel, and capecitabine) followed by 5-FU-IMRT was administered to patients with borderline resectable pancreatic cancer. The utility of computed tomography (CT), endoscopic ultrasound (EUS), positron emission tomography (PET), and CA 19-9 during diagnostic workup and assessment of response was also examined. Seventeen patients with borderline resectable pancreatic cancer received a median of three cycles of neoadjuvant GTX induction chemotherapy followed by 5-FU-IMRT with dose painting. CA 19-9, CT mass size, and PET SUV were examined before and after neoadjuvant treatment. Diagnostic EUS and CT scans displayed similar mean mass sizes and extent of vascular involvement. Eight of the 17 patients achieved an R0 resection. Median CA 19-9 levels, CT mass size, and PET SUV all significantly decreased after neoadjuvant therapy. The median progression-free survival and overall survival were 10.48 and 15.64 months, respectively. Six patients are still alive. It was concluded that neoadjuvant GTX induction chemotherapy followed by 5-FU-IMRT shows promise in improving the likelihood of resectability with negative margins in borderline resectable pancreatic cancer. CT and EUS play complimentary roles during diagnostic workup. CT scans, CA 19-9, and PET scans are useful in judging response to neoadjuvant therapy [379].

Neoadjuvant therapy has been used to improve survival in operable pancreatic cancer. The authors' objective was to compare long-term outcomes in patients receiving neoadjuvant versus adjuvant therapy for resectable pancreatic adenocarcinoma. The California Cancer Surveillance Program for Los Angeles County retrospectively identified 458 patients with nonmetastatic pancreatic adenocarcinoma who underwent definitive pancreatic resection and received systemic chemotherapy between 1987 and 2006. The cohort was grouped by timing of systemic therapy: neoadjuvant or adjuvant. Clinicopathologic characteristics and overall survival were compared. Of the 458 patients, 39 (9 %) received neoadjuvant therapy, and 419 (92 %) received adjuvant therapy. There was a significantly lower rate of lymph node positivity in the neoadjuvant group (45 % vs 65 %) despite a higher rate of extrapancreatic tumor extension. On Kaplan-Meier analysis, the neoadjuvant group had significantly better overall survival compared with the adjuvant group (median survival, 34 vs 19 months). Overall survival was also improved in the neoadjuvant therapy patients with extrapancreatic disease (median survival, 31 vs 19 months). On multivariate Cox regression

analysis, neoadjuvant therapy was an independent predictor of improved survival (hazard ratio, 0.57; 95 % confidence interval 0.37 to 0.89). In this population-based study to compare neoadjuvant versus adjuvant treatment strategies in resectable pancreatic cancer neoadjuvant therapy is associated with a lower rate of lymph node positivity and improved overall survival and should be considered an acceptable alternative to the surgery-first paradigm in operable pancreatic cancer [380].

To evaluate the safety of 1 week of chemoradiation with proton beam therapy and capecitabine followed by early surgery 15 patients with localized resectable, pancreatic adenocarcinoma of the head were enrolled from 2006 to 2008. Patients received radiation with proton beam. In dose level 1, patients received 3 GyE × 10 (Week 1, Monday-Friday; Week 2, Monday-Friday). Patients in Dose Levels 2 to 4 received 5 GyE × 5 in progressively shortened schedules: level 2 (Week 1, Monday, Wednesday, and Friday; Week 2, Tuesday and Thursday), Level 3 (Week 1, Monday, Tuesday, Thursday, and Friday; Week 2, Monday), Level 4 (Week 1, Monday through Friday). Capecitabine was given as 825 mg/m² b.i.d. Weeks 1 and 2 Monday through Friday for a total of 10 days in all dose levels. Surgery was performed 4 to 6 weeks after completion of chemotherapy for Dose Levels 1 to 3 and then after 1 to 3 weeks for Dose Level 4. Three patients were treated at Dose Levels 1 to 3 and 6 patients at Dose Level 4, which was selected as the MTD. No dose limiting toxicities were observed. Grade 3 toxicity was noted in 4 patients (pain in 1; stent obstruction or infection in 3). Eleven patients underwent resection. Reasons for no resection were metastatic disease (3 patients) and unresectable tumor (1 patient). Mean postsurgical length of stay was 6 days (range, 5-10 days). No unexpected 30-day postoperative complications, including leak or obstruction, were found. It was concluded that preoperative chemoradiation with 1 week of proton beam therapy and capecitabine followed by early surgery is feasible. A phase II study is underway [381].

5FU and cisplatin

Several phase II studies have shown the feasibility of neoadjuvant chemoradiation regimens for resectable localized pancreatic adenocarcinoma. However, there is to date no completed phase III study to validate this approach and treatment effects evaluation still remains an active area of investigation. From the mature results of the SFRO-FFCD 9704 trial, it was explored the antitumoral effect of a 5-fluoro-uracil and cisplatin-based preoperative chemoradiation regimen, with a special highlight on the histopathological response and performed a literature review. Treatment consisted of concurrent radiotherapy (50 Gy within five weeks) and chemotherapy with 5-fluoro-uracil (300 mg/m²/day, five days/week, weeks 1-5) and cisplatin (20mg/m²/day, days 1-5 and 29-33), followed by surgical resection of the pancreatic tumour in patients without progression. In all, 41 patients were enrolled, 26 patients (63 %) underwent surgical resection with curative intent and 21 (81 %) had R0 resection. A total of 13 of 26 specimens (50 %) presented a major pathologic response (≥ 80 % of severely degenerative cancer cells), with one complete pathologic response. The local recurrence and two-year survival rates were 4 and 32 percent, respectively, for the 26 operated patients. The results suggest that preoperative chemoradiation provides antitumoral effect associated with major histopathological response in 50% of patients and a high R0 resection rate. Evaluation of histopathological response to neoadjuvant chemoradiation may serve as a surrogate marker for treatment efficacy and further research is needed to determine new prognostic and predictive factors of treatment response [382].

Adjuvant therapy

To improve surgical results after resection of pancreatic cancer, clinical trials of postoperative adjuvant treatment have been aggressively performed worldwide. In the USA, postoperative chemoradiation therapy is supported on the basis of the results of the Gastrointestinal Tumor Study Group (GITSG) trial published in 1985. In Europe, chemotherapy was approved as

postoperative adjuvant therapy based on the results of the European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial published in 2004 and Charité Onkologie (CONKO)-001 study published in 2007. As in Europe, postoperative chemotherapy is recommended in Japan based on the results of the Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer-02 (JSAP-02) trial published in 2009. In recent years, gemcitabine has been recognized as the first choice for adjuvant chemotherapy after surgery. Clinical trials with gemcitabine, fluorouracil, and molecular targeting agents are currently under way [383].

To evaluate the efficacy of adjuvant chemoradiation therapy (CRT) for pancreatic adenocarcinoma patients ≥ 75 years of age a study group of 655 patients who underwent pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma at the Johns Hopkins Hospital over a 12-year period (1993 to 2005) was addressed. Demographic characteristics, comorbidities, intraoperative data, pathology data, and patient outcomes were collected and analyzed by adjuvant treatment status and age ≥ 75 years. Cox proportional hazards analysis determined clinical predictors of mortality and morbidity. It was identified 166 of 655 (25 %) patients were ≥ 75 years of age and 489 of 655 patients (75 %) were <75 years of age. Forty-nine patients in the elderly group (30 %) received adjuvant CRT. For elderly patients, node-positive metastases, poor/anaplastic differentiation, and undergoing a total pancreatectomy predicted poor survival. The 2-year survival for elderly patients receiving adjuvant therapy was improved compared with surgery alone (49 % vs 32 %); however, 5-year survival was similar (12 % vs 20 %, respectively). After adjusting for major confounders, adjuvant therapy in elderly patients had a protective effect with respect to 2-year survival (relative risk 0.58), but not 5-year survival (RR 0.80). Among the nonelderly, CRT was significantly associated with 2-year survival (RR 0.60) and 5-year survival (RR 0.69), after adjusting for confounders. It was concluded that adjuvant therapy after PD is significantly associated with increased 2-year but not 5-year survival in elderly patients [384].

The aim of one study was to evaluate the adjuvant chemotherapy using (GEM) for resected pancreatic cancer. It was investigated 69 patients who had undergone curative operations for pancreatic cancer. They were classified into two groups of patients using GEM (group A: 37) and patients with surgery alone (group B: 32) between 2009 and 1998. Outcomes, including disease-free survival (DFS), median survival time (MST), and adverse events were reported retrospectively. Patients assigned to the gemcitabine group received GEM at a dose of 800 mg/m² on days 1, 8 and 15, every 4 weeks for 5 cycles. DFS and MST did not differ significantly between group A and group B (DFS; group A: 10 vs group B 8 months, MST; group A: 21.7 vs group B 16 months). The estimated overall survival rates at 3 and 5 years were 40 and 26 percent, respectively, in group A, and 13 and 13 percent in group B. Grade 3 or 4 toxicity revealed 8 percent with leucopenia, 3 percent with thrombocytopenia, and 3 percent with nausea. It was concluded that adjuvant chemotherapy using gemcitabine for resected pancreatic cancer contributes to prolonged DFS, MST, and estimated overall survival [385].

Preoperative CA 19-9 as prognostic factor in adjuvant chemotherapy

To evaluate preoperative CA 19-9 level as a prognostic factor in patients with resected adenocarcinoma of the pancreas it was retrospectively reviewed the cases of consecutive patients with pancreatic adenocarcinoma who had CA 19-9 measured preoperatively and underwent potentially curative resection at Mayo Clinic from 1995 to 2005. Patients who died within 30 days of resection were excluded. Search of the database identified 226 consecutive patients who met all the inclusion criteria. Adjuvant therapy was concurrent chemoradiotherapy (CCRT) in 122 patients, CCRT followed by chemotherapy in 23 patients, chemotherapy alone in 6 patients, and none in 69 patients. Median follow-up for surviving patients was 2.1 years. Median survival in all patients was 1.6 years. Patients with a high preoperative CA 19-9 level (defined as ≥ 180 U/mL) had a significantly greater chance of having pathologic T3-T4 disease, positive lymph nodes, and histologic grade 3 or 4. In multivariate analysis, a high preoperative CA 19-9 level and R1-R2 margin status were

associated with decreased survival. Overall survival was increased for patients who received adjuvant CCRT (vs those who did not) and for patients with high preoperative CA 19-9 level who received adjuvant CCRT (vs those who did not). In patients with resected adenocarcinoma of the pancreas, high preoperative CA 19-9 level was associated with adverse pathologic features and poorer survival. Adjuvant CCRT was associated with a significant survival benefit in patients with high preoperative CA 19-9 but not in those with low CA 19-9 [386].

Targeted therapies

Targeted therapies and personalized cancer care are based on genetic markers. Despite remarkable progress, developing companion diagnostic testing remains challenging for many treatments. Counting circulating tumor cells (CTCs) may be the key to profiling metastases. Although disseminated tumor cells and CTCs can both yield information on tumor profiles, disseminated tumor cells reside in the bone marrow, making access difficult. CTCs are easily accessible in patient blood for sampling but are rare and fragile. Magnetic beads coated with antiepithelial cell adhesion molecules isolate and characterize different populations of cancer cells that tumors and their metastases release. There is a beginning to understand the variations of the pancreatic cancer genome. Not only is this leading to an increasing number of targeted therapies in development, but it also raises questions on whether and when oncologists should encourage familial genetic screening. Although pancreatic cancers have a low frequency of driver mutations CTCs can be used as a measure of tumor burden and reveal changes more rapidly than computed tomography scans. Between 10 and 20 percent of patients with pancreatic intraductal papillary mucinous neoplasms have an underlying genetic disposition to it and other cancers. Deleterious causative germline mutations of BRCA2 and PALB2 are associated with familial pancreatic cancer [387].

Pancreatic cancer treatment remains a challenge for clinicians and researchers. Despite undisputable advances in the comprehension of the molecular mechanisms underlying cancer development and progression, early disease detection and clinical management of patients has made little, if any, progress in the past 20 years. Clinical development of targeted agents directed against validated pathways, such as the EGF/EGF receptor axis, the mutant KRAS protein, MMPs, and VEGF-mediated angiogenesis, alone or in combination with gemcitabine-based standard chemotherapy, has been disappointing. One review explored the preclinical rationale for clinical approaches aimed at targeting the TGF-beta, IGF, Hedgehog, Notch and NF- κ B signaling pathways, to develop innovative therapeutic strategies for pancreatic cancer. Although some of the already clinically explored approaches (particularly EGFR and KRAS targeting) deserve further clinical consideration, by employing more innovative and creative clinical trial designs than the gemcitabine-targeted agent paradigm that has thus far invariably failed, the targeting of emerging and relatively unexplored signaling pathways holds great promise to increase the understanding of the complex molecular biology and to advance the clinical management of pancreatic cancer [388].

Locally advanced pancreatic cancer

At diagnosis, 30 to 35 percent of patients with pancreatic cancer present with locally advanced unresectable disease (LAPC). The natural history of this stage of cancer may be different from that of metastatic disease with an important contribution from complications of local spread. A recent rapid autopsy series of patients with pancreatic cancer from Johns Hopkins Hospital identified 30 percent who succumbed to locally destructive disease without evidence of progression at distant sites. Chemoradiotherapy has been a component of therapy for LAPC based on a few small studies in the 1980s that used ineffective systemic therapies and older radiation techniques. As it was developed better systemic therapies for

this disease, refine radiation techniques, and begin to better understand its molecular biology, one important question is how to optimize the multimodality therapy of LAPC. Led by the Eastern Cooperative Oncology Group (ECOG) in the United States, one study tested the superiority of concurrent gemcitabine and radiation therapy over gemcitabine alone. Unfortunately, the study was terminated because of poor patient accrual with only 74 patients out of a planned total of 316. The overall survival of patients – the primary end point of this study – was superior in those treated with concurrent weekly gemcitabine (600 mg/m²) and radiation (50.4 Gy) compared with those who received standard dose and schedule of gemcitabine alone (11 months vs 9 months). The survival curves started to separate after 6 months on study when the majority of patients in both arms had progressive disease and had completed most of their planned therapy. Because of the limited statistical power due to incomplete patient accrual, therefore, these results would appear not to support for a level of evidence that impacts standard of care. The modest benefit (at best) for chemoradiation therapy inferred from this study and from earlier reports on fluorouracil combined with radiation is probably real and more a function of the limited efficacy of systemic therapy in pancreatic cancer than the impact of radiation itself. In a disease with so many systemic manifestations, it is hard to see radiation therapy significantly impact the natural history of this disease without obtaining some control of metastatic disease by the systemic therapy. Therefore, there is an urgent need to test newer and novel treatment strategies in patients with pancreatic cancer including those with LAPC. One such advance in the systemic therapy of pancreatic cancer appears to be a FOLFIRONOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen that resulted in a significant improvement in the survival of patients with metastatic disease in a phase III study from Europe. While there is much interest to incorporate FOLFIRONOX into the multimodality treatment of patients with pancreatic cancer, there is no experience on the benefit versus risks of using FOLFIRONOX in patients with LAPC; of particular concern are abnormalities in liver function that will increase toxicity to this regimen in patients recovering from obstructive jaundice. Studies are just getting underway to determine the role of FOLFIRONOX in patients with LAPC (and those with borderline resectable pancreatic cancer as well) around the world. The objectives of these studies would be primarily to demonstrate a survival benefit by using this regimen. In addition, an improvement in locoregional control and resectability will also be of interest given the higher objective response rates seen with FOLFIRONOX. The focus of the newer generation of studies in LAPC is on improving systemic therapy and on testing of targeted agents. The majority of oncologists will continue to recommend the incorporation of radiation therapy in the treatment of LAPC. However, the small benefit of radiation therapy in an average patient with LAPC indicates that only a subgroup of patients benefit from radiation therapy while there will be those who will not only derive no benefit but be harmed by its toxicities. Objective criteria to select patients for radiation therapy in clinical practice and to stratify patients in clinical trials are limited at this time. Investigators have adopted a strategy of induction chemotherapy for 3 to 6 months followed by chemoradiotherapy, sparing those who develop metastatic disease while on chemotherapy. This biologic testing of patients to select patients for radiation treatment is based on limited data from retrospective analyses. The ongoing LAP-07 study in Europe is a prospective study that is partly asking this question. New studies in patients with LAPC in the United States are increasingly adopting a strategy of induction systemic therapy, especially in the testing of targeted agents. Nevertheless, study design must account for the radiation effect in assigning study end points. For this reason overall survival may continue to be the primary end point in studies in LAPC. In the absence of reliable clinicopathologic criteria to select patients with LAPC who may benefit from radiation therapy we need to develop molecular markers that are associated with disease biology that would predict disease behavior in a given patient. The absence of tumor suppressor gene DPC4 expression by immunoblotting was associated with death from metastatic disease whereas its expression was in the majority of patients who died of complications of locoregional disease. Similar conclusions were reached from a study on a small series of patients with LAPC that was recently reported. Although this may be a first step in personalizing treatment based on a molecular marker it is unlikely that a mutation

in a single gene will reliably characterize disease behavior given the well-documented molecular complexity in pancreatic adenocarcinoma. Multiple gene markers or microRNA signatures may be more informative in this respect and must be actively investigated in future clinical trials [389].

Gemcitabine

Gemcitabine sensitivity

Gemcitabine has been a first-line chemotherapy agent for advanced pancreatic cancer. Due to our lack of understanding of the genetic determinants of gemcitabine sensitivity in pancreatic cancer, the therapeutic effectiveness of gemcitabine chemotherapy is typically unpredictable. Using a genome-wide and piggyBac transposon-based genetic screening platform, it was identified the PVT1 gene as a regulator of gemcitabine sensitivity and showed that functional inactivation of the PVT1 gene led to enhanced Gemcitabine sensitivity in human pancreatic cancer ASPC-1 cells. The integration of the piggyBac transposon-based vector system into intron 3 of PVT1 was within a common site of oncogenic retroviral insertions and chromosomal translocations. PVT1 is a non-protein encoding gene; the genomic arrangement of PVT1 and its co-amplification with MYC have been implicated in the tumorigenesis of a variety of cancers. The molecular mechanism of PVT1 transcripts in gene regulation remains a puzzle. It was demonstrated that overexpression of a full length PVT1 cDNA in the antisense orientation reconstituted enhanced sensitivity to gemcitabine in naïve ASPC-1 cells, whereas overexpression of a full length PVT1 cDNA in the sense orientation resulted in decreased sensitivity to Gemcitabine. The results identified PVT1 as a regulator of gemcitabine sensitivity in pancreatic cancer cells and validated the genome-wide genetic screening approach for the identification of genetic determinants as well as potential biomarkers for the rational design of Gemcitabine chemotherapies for pancreatic cancer [390].

Gemcitabine nephrotoxicity

Among several chemotherapeutic agents, gemcitabine is a first-line drug for pancreatic cancer. Because no other chemotherapeutic agent has been able to surpass the treatment outcome of gemcitabine monotherapy in previous studies, gemcitabine still plays a critical role in the treatment for pancreatic cancer either in monotherapy or in combination with other chemotherapeutic agent(s). When patients respond well to gemcitabine, there are several patients who survive more than a year. In these cases, avoiding the serious adverse effects of chemotherapy and keeping good performance statuses of patients are factors that determine the prognosis of patients. It has previously reported two patients with pancreatic cancer who responded well to gemcitabine monotherapy but died of acute renal failure due to acute tubulointerstitial nephritis. In both cases, crystal deposits were recognized in renal tubules at necropsy, and thus, it was speculated that the precipitation of gemcitabine itself or its metabolites in renal tubules after chemotherapy caused acute tubulointerstitial nephritis. Based on these findings, it has been developed a new gemcitabine chemotherapy regimen followed by 1000 mL of intravenous fluid infusion. All of the patients with advanced pancreatic cancer who received gemcitabine monotherapy, in which a postmortem necropsy was performed were included in this study. Patients were divided into three groups: high cumulative dose of gemcitabine group (n=2), low cumulative dose of gemcitabine group (n=2), and high cumulative dose of gemcitabine followed by intravenous fluid infusion group (n=2). In the high cumulative dose of gemcitabine group, two patients died of acute renal failure. The low cumulative dose of gemcitabine group was given a cumulative gemcitabine dose of less than 10 g/m² body surface area. The third group was treated with a high cumulative dose of gemcitabine chemotherapy followed by an infusion of 1000 mL of intravenous lactated Ringer's solution. For the treatment of advanced pancreatic cancer, two patients were treated with gemcitabine monotherapy (high-cumulative dose group). In both cases, because renal function of these patients was progressively decreased during

gemcitabine treatment, chemotherapy was discontinued (case 1, 17 g/m²; case 2, 30 g/m², respectively). These patients died of acute renal failure as was reported previously in detail. There were indications that gemcitabine caused renal dysfunction in a dose-dependent manner, even in patients who received small amounts of gemcitabine (3-4 cycles) and show no evidence of renal dysfunction clinically. Clinically, oliguria and high serum uric acid level were remarkable in these patients. It was hypothesized that it was caused by the dysfunction of uric acid transporters and water channels expressed in renal tubules. It was indicated that the aberrant expression of membrane proteins in renal tubules causes renal dysfunction in the high cumulative dose of gemcitabine group [391].

Pulmonary side effects

Although there are several reports concerning gemcitabine-induced interstitial lung disease (ILD), the risk factors for ILD are not well known. In addition, data comparing the incidence and pattern of ILD associated with gemcitabine treatment in patients with non-small-cell lung cancer (NSCLC) versus those with pancreatic cancer are scarce. It was reviewed clinical records of 118 patients treated with gemcitabine between 2004 and 2010. The radiographic findings and other relevant clinical data were reviewed to identify patients who had developed ILD associated with gemcitabine treatment. Out of these 118 patients, it was identified 62 patients with NSCLC (group A) and 56 patients with pancreatic cancer (group B), which were then analysed. After gemcitabine administration, ILD was detected in 9 out of the total 118 patients (8 %). Three patients had grade 2 ILD and 6 patients had grade 3 ILD. Multivariate analysis revealed that prior thoracic radiotherapy (odds ratio: 26.3) and pre-existing pulmonary fibrosis (odds ratio 6.5) were correlated with ILD occurrence, but the incidence of ILD was not different between groups A and B. The median dose of gemcitabine administered till the manifestation of ILD tended to be lower in group A than in group B. It was concluded that prior thoracic radiotherapy and pre-existing pulmonary fibrosis were correlated with higher ILD rate in gemcitabine-treated patients. ILD incidence did not differ between NSCLC and pancreatic cancer patients, which may be due to the differences in treatment strategy and tumour properties [392].

The combination of docetaxel and gemcitabine was tested in several studies in patients with lung, breast, and pancreatic cancers and other tumor entities. Some studies reported cases of severe or even fatal pulmonary toxicity that led to early termination of some trials. It was created a meta-analysis model of published studies to identify explanatory factors for docetaxel-gemcitabine-dependent pulmonary toxicity. It was searched MEDLINE/Pubmed, EMBASE, and Cochrane Clinical Trials database for prospective full-text studies that used a schedule of docetaxel and gemcitabine to treat a malignant disease. It was performed a meta-analysis for proportions using the arcsine transformation and a meta-regression using a generalized linear mixed model based on a binomial distribution and a logit link. It was included 103 trials with 113 treatment arms comprising 5,065 patients (major entities included non-small cell lung cancer (n=2,550), breast cancer (n=1,119), pancreatic cancer (n=466), and urothelial cancer (n=161)). For the incidence of severe lung toxicity (common toxicity criteria, CTC, grades 3-5), it was found a combined estimate of 2.7 percent. The estimate for the proportion of fatal cases was 0.35 percent. It was found that the sequence of the chemotherapy schedule had no influence on the incidence of severe pulmonary adverse events nor did the study phase, treatment line or ethnicity of the participants. It was found that patients with breast cancer, compared to lung cancer patients, developed severe lung toxicity less frequently (OR 0.18). It could not be demonstrated that a particular chemotherapy sequence of docetaxel-gemcitabine is associated with excess pulmonary toxicity. Patients with lung cancer are at a higher risk for severe pulmonary side effects with docetaxel-gemcitabine than are patients with breast cancer [393].

Doubling time

To depict treatment response to chemoradiotherapy by comparing tumor growth rate between treated and untreated patients and to compare depicted response with objective

response according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guideline. This Health Insurance Portability and Accountability Act-compliant, retrospective study was approved by the institutional review board. Volume doubling time (DT) of histologically confirmed locally advanced pancreatic adenocarcinoma was calculated in 16 patients treated with chemoradiotherapy and 10 untreated patients by incorporating interscan interval (Δt) and tumor volume at baseline (V_0) and follow-up (V_1) obtained by semiautomated segmentation into the following equation: $DT = \Delta t \cdot \log 2 / \log (V_1/V_0)$. Reciprocal of doubling time (RDT), which is the linear representation of tumor growth rate, was calculated by use of the following equation: $RDT = 365/DT$. The lowest RDT value of 2.42 in untreated patients was considered as the cutoff value for depiction of treatment response. Depicted response rate was defined as the proportion of patients with an RDT value of less than 2.42. Depicted response was compared with objective response according to the RECIST 1.1 guideline. There was a significant difference in mean RDT between treated (range, -7.12 to 3.27; mean, -1.27; median, -1.30) and untreated (range, 2.42 to 10.74; mean, 5.33; median, 4.26) patients. Reciprocal of doubling time was less than 2.42 in 14 treated patients, which corresponded to a depicted response rate of 88 percent as opposed to the objective response rate of 19 percent according to the RECIST 1.1 guideline and carbohydrate antigen 19-9 response rate of 63 percent. Carbohydrate antigen 19-9 response was concordant with RDT and RECIST response in 12 patients (75 %) and 9 patients (56 %), respectively. There was a significant difference between depicted response according to RDT and objective response according to RECIST. Reciprocal of doubling time might serve as a valuable biomarker for evaluation of treatment response when depiction of small changes in tumor size is concerned [394].

Experimental

As activation and overexpression of the cholecystokinin-2 (CCK-2)/gastrin receptor can lead to carcinogenesis, it has been explored as a therapeutic target in pancreatic cancer. We demonstrated that Z-360, a CCK-2/gastrin receptor antagonist, combined with gemcitabine prolonged survival and reduced gemcitabine-induced vascular endothelial growth factor (VEGF) expression in a pancreatic carcinoma orthotopic xenograft mouse. In this study, we investigated the role of the CCK-2/gastrin signaling pathway on gemcitabine-induced VEGF expression in PANC-1 human pancreatic carcinoma cells. In PANC-1 cells treated with Z-360, anti-gastrin IgG or kinase inhibitors, the gene expression levels were analyzed by quantitative real-time RT-PCR, and the protein levels of Akt and phosphorylated Akt (p-Akt) in cellular extracts were measured by ELISA. Gemcitabine-induced expression of VEGF and hypoxia-inducible factor-1 alpha (HIF-1 alpha) were suppressed by the treatment with an anti-gastrin antibody. In addition, VEGF and HIF-1 alpha gene expression was inhibited by treatment with an inhibitor of phosphatidylinositol 3-kinase (PI3K), which is involved in the downstream signaling pathway of the CCK-2/gastrin receptor, and was also suppressed by treatment with Z-360. Moreover, although Akt phosphorylation was increased by treatment with gemcitabine, this elevation was partially, but significantly, inhibited by an exposure of Z-360. This means that gemcitabine might induce gene expression of VEGF via the PI3K/Akt signaling pathway in the downstream of the CCK-2/gastrin receptor. The suppression of the CCK-2/gastrin signaling pathway by treatment with Z-360 could be a useful approach for potentiating prolonged survival of pancreatic cancer patients receiving gemcitabine therapy [395].

Gemcitabine plus 5FU plus folinic acid

This open-label, multi-center phase II study investigated the efficacy and safety of the combination of 5-fluorouracil (5-FU)/folinic acid (FA) plus gemcitabine (GFF) in patients with advanced pancreatic cancer. The study is based on our completed dose finding phase I trial. A total of 90 patients were recruited between 2000 and 2002 to receive 5-FU 750 mg/m² (24 h, i.v.), FA 500 mg/m² (2 h, i.v.) and gemcitabine 1,000 mg/m² (30 min, i.v.) on days 1, 8, 15, and 22. Treatment was repeated on day 43 until disease progression. The primary

objective was the 1-year survival rate. The 1-year survival rate was 25 percent (95 % confidence interval 16 to 34), median overall survival was 7 months (95 % confidence interval 5 to 8), 9 patients showed partial responses (PR) so that the overall response rate was 10 percent. Overall control rate (PR + stable disease for at least 6 months) was 56 percent. Median time to progression was 5 months. In 402 GFF cycles, it was observed adverse events grade 3 in up to 10 percent of patients and grade 4 below 5 percent of patients. The GFF combination appears to be effective and well tolerated. This intravenous regimen represents an intensified therapy with low frequency of toxicities and seems to be convenient for patients who are unable to get oral anti-neoplastic medication [396].

Gemcitabine plus oxaliplatin plus bevacizumab

The gemcitabine and oxaliplatin (GEMOX) has yielded among the longest progression-free survival durations in patients with advanced pancreatic cancer (APC). It was postulated that adding bevacizumab would increase the effectiveness of GEMOX. Eligible patients had stage III or IV pancreatic cancer, ECOG PS 0-2, and no prior gemcitabine. Treatment included 1,000 mg/m² intravenous gemcitabine over 100 min on day 1, 10 mg/kg intravenous bevacizumab on day 1, and 100 mg/m² oxaliplatin given on day 2. Cycles were repeated every 2 weeks. CT imaging was performed every 6 weeks. Fifty patients were enrolled: 14 had stage III disease, the remainder stage IV. Median age was 59 years. Forty-five patients were ECOG 0-1. The grade 3-4 toxicity rate was 94 percent; fatigue (47 %) and nausea (40 %) were frequent. One patient died after a bowel perforation; a second died of a CVA. The median PFS was 5 months; median survival was 12 months; 1 year survival was 42 percent. Locally advanced patients lived 13 months; metastatic patients lived 11 months. Patients developing grade 3 hypertension were more likely to have a radiologic response; survival among the top and bottom quintiles of hypertension was 15 and 6 months, respectively. Survival correlated with baseline CA 19-9 and radiologic response. The overall response rate was 36 percent; 34 percent demonstrated stable disease. It was concluded that GEMOX/bevacizumab regimen demonstrated an excellent median overall survival but did not meet the objective of a 14 month median survival. Toxicity was significant. It was not recommended further evaluation of this regimen [397].

Gemcitabine ± paclitaxel

The trial objectives were to identify the maximum-tolerated dose (MTD) of first-line gemcitabine plus nab-paclitaxel in metastatic pancreatic adenocarcinoma and to provide efficacy and safety data. Additional objectives were to evaluate positron emission tomography (PET) scan response, secreted protein acidic and rich in cysteine (SPARC), and CA19-9 levels in relation to efficacy. Subsequent preclinical studies investigated the changes involving the pancreatic stroma and drug uptake. Patients with previously untreated advanced pancreatic cancer were treated with 100, 125, or 150 mg/m² nab-paclitaxel followed by gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 28 days. In the preclinical study, mice were implanted with human pancreatic cancers and treated with study agents. A total of 20, 44, and three patients received nab-paclitaxel at 100, 125, and 150 mg/m², respectively. The MTD was 1,000 mg/m² of gemcitabine plus 125 mg/m² of nab-paclitaxel once a week for 3 weeks, every 28 days. Dose-limiting toxicities were sepsis and neutropenia. At the MTD, the response rate was 48 percent, with 12 median months of overall survival (OS) and 48 percent 1-year survival. Improved OS was observed in patients who had a complete metabolic response on 18F-fluorodeoxyglucose PET. Decreases in CA19-9 levels were correlated with increased response rate, progression-free survival, and OS. SPARC in the stroma, but not in the tumor, was correlated with improved survival. In mice with human pancreatic cancer xenografts, nab-paclitaxel alone and in combination with gemcitabine depleted the desmoplastic stroma. The intratumoral concentration of gemcitabine was increased by 2.8-fold in mice receiving nab-paclitaxel plus gemcitabine

versus those receiving gemcitabine alone. The regimen of nab-paclitaxel plus gemcitabine has tolerable adverse effects with substantial antitumor activity, warranting phase III evaluation [398].

Gemcitabine and S-1

Pancreatic acinar cell carcinoma is rare, and its incidence is less than 1 percent of all the malignant pancreatic tumors. Little is reported on effectiveness of chemotherapy. It was reported a 64-year-old male patient with pancreatic acinar cell carcinoma and a giant metastatic liver tumor, which responded to combination chemotherapy with gemcitabine (GEM) and peroral S-1 administration. The patient had upper abdominal pain and hypervascular tumors in liver (15 cm in diameter) and pancreas tail (3 cm in diameter), which were detected by an enhanced abdominal computed tomography (CT) scan, and was admitted for further examination. Abdominal angiography, FDG-positron emission tomography (PET), and liver tumor biopsy led to a diagnosis of pancreatic acinar cell carcinoma in the pancreas tail with liver metastasis. The patient was then treated with combination chemotherapy, which consisted of intravenous infusion of GEM and peroral administration of S-1, and the metastatic liver tumor was markedly reduced (partial response in RECIST). Although the prognosis of patients with unresectable pancreatic acinar cell cancers is generally unfavorable, it is suggested that the GEM/S-1 combination chemotherapy is effective for these patients' treatment [399].

The aim of one multicenter phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer. Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m² over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m² twice daily from days 1 to 14, repeated every 3 weeks. A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44 percent (95 % confidence interval 31 to 59 %). The median progression-free survival was 6 months (95 % confidence interval 4 to 7 months) and the median overall survival was 10 months (95 % confidence interval 9 to 11 months) with a 1-year survival rate of 33 percent. The major Grade 3-4 toxicities were neutropenia (80 %), leucopenia (59 %), thrombocytopenia (22 %), anorexia (17 %) and rash (7 %). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥ Grade 3. It was concluded that gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing [400].

Gemcitabine and erlotinib

In one article, it was reviewed current first-line treatments for metastatic pancreatic adenocarcinoma focusing on randomized studies. Among the numerous randomized phase III studies comparing gemcitabine as single agent to gemcitabine combined to a new agent, only the gemcitabine-erlotinib combination has shown a small, but statistical improvement in survival. A trend to better survival was also observed with a gemcitabine-capecitabine regimen. The use of low-weight heparin may be of value to reduce venous thromboembolic events. In selected patients with good performance status ECOG 0-1, the Folfirinox regimen, when compared with gemcitabine, was associated with more toxicities and significantly increased median survival from 7 to 11 months. Gemcitabine (with or without erlotinib or capecitabine) is still the reference treatment in patients with ECOG performance status 2.

Folfirinox is a new more toxic and more efficient regimen that may be considered in patients with good performance status [401].

Gemcitabine plus erlotinib

To evaluate the feasibility, toxicity and efficacy of the combination regimen consisting of gemcitabine-FDR infusion plus erlotinib, in advanced pancreatic cancer patients. Forty-two patients with histologically confirmed, locally advanced or metastatic pancreatic cancer were included in this phase II trial. Main objectives were to assess the efficacy and safety of this regimen. Therapeutic regimen consisted of gemcitabine 1,200 mg/m² in 120-min infusion on days 1, 8 and 15, plus erlotinib 100 mg orally once daily. Cycles were repeated every 28 days. A total of 160 courses of gemcitabine-FDR erlotinib were administered (median 3.8 courses per patient). The most common grade 3-4 AEs were neutropenia (21 %), thrombocytopenia (10 %), skin rash (10 %) and asthenia (10 %). Complete response was achieved in one patient (2 %) and 11 (26 %) achieved a partial response. Stable disease and progression disease were observed in 11 patients (26 %) and 19 (45 %), respectively. Median time to progression was 5 months (95 % confidence interval 4-6 months) and median overall survival was 8 months. One-year survival rate was 35 percent. It was concluded that a regimen consisting of gemcitabine-FDR infusion plus erlotinib is active and well tolerated in APC patients. However, the results do not justify the conduct of a Phase III trial [402].

Gemcitabine ± dithiocarbamate derivatives

Pancreatic adenocarcinoma is a common malignancy that remains refractory to all available therapies, including the gold standard drug gemcitabine (GEM). It was investigated the effect of the combination of GEM and each of the ionophore compounds pyrrolidine dithiocarbamate (PDTC) and disulfiram (DSF; 1-(diethylthiocarbamoyldisulfanyl)-N,N-diethylmethanethioamide) on p53(-/-) pancreatic adenocarcinoma cell growth. PDTC or DSF synergistically inhibited cell proliferation when used in combination with GEM by inducing apoptotic cell death. This effect was associated with an increased mitochondrial O₂ production and was further enhanced by zinc ions. Basal levels of mitochondrial O₂ or manganese superoxide dismutase (MnSOD) strictly correlated with the IC₅₀ for GEM or the percentage of synergism. Thus, the most relevant values of the antiproliferative synergism were obtained in GEM-resistant pancreatic adenocarcinoma cell lines. Interestingly, the GEM-sensitive T3M4 cells transfected with MnSOD expression vector showed mitochondrial O₂ and IC₅₀ for GEM similar to those of resistant cell lines. In vivo experiments performed on nude mice xenotransplanted with the GEM-resistant PaCa44 cell line showed that only the combined treatment with GEM and DSF/Zn completely inhibited the growth of the tumoral masses. These results and the consideration that DSF is already used in clinics strongly support the GEM and DSF/Zn combination as a new approach to overcoming pancreatic cancer resistance to standard chemotherapy [403].

Gemcitabine and radiation

A phase II trial evaluated the toxicity, local control, and overall survival in patients treated with sequential gemcitabine and linear accelerator-based single-fraction stereotactic body radiotherapy (SBRT). Twenty patients with locally advanced, nonmetastatic pancreatic adenocarcinoma were enrolled on this prospective single-institution, institutional review board-approved study. Gemcitabine was administered on days 1, 8, and 15, and SBRT on day 29. Gemcitabine was restarted on day 43 and continued for 3-5 cycles. SBRT of 25 Gy in a single fraction was delivered to the internal target volume with a 2-3-mm margin using a nine-field intensity-modulated radiotherapy technique. Respiratory gating was used to account for breathing motion. Follow-up evaluations occurred at 4-6 weeks, 10-12 weeks, and every 3 months after SBRT. All patients completed SBRT and a median of five cycles of

chemotherapy. Follow-up for the 2 remaining alive patients was 25 and 36 months. No acute grade 3 or greater nonhematologic toxicity was observed. Late grade 3 or greater toxicities occurred in 1 patient (5 %) and consisted of a duodenal perforation (G4). Three patients (15 %) developed ulcers (G2) that were medically managed. Overall, median survival was 12 months, with 1-year survival of 50 percent and 2-year survival of 20 percent. Using serial computed tomography, the freedom from local progression was 94 percent at 1 year. It was concluded that linear accelerator-delivered SBRT with sequential gemcitabine resulted in excellent local control of locally advanced pancreatic cancer [404].

Gemcitabine ± radiation

The purpose of this trial was to evaluate the role of radiation therapy with concurrent gemcitabine (GEM) compared with GEM alone in patients with localized unresectable pancreatic cancer. Patients with localized unresectable adenocarcinoma of the pancreas were randomly assigned to receive GEM alone (at 1,000 mg/m²/wk for weeks 1 to 6, followed by 1 week rest, then for 3 of 4 weeks) or GEM (600 mg/m²/wk for weeks 1 to 5, then 4 weeks later 1,000 mg/m² for 3 of 4 weeks) plus radiotherapy (starting on day 1, 1.8 Gy/Fx for total of 50.4 Gy). Measurement of quality of life using the Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire was also performed. Of 74 patients entered on trial and randomly assigned to receive GEM alone (arm A; n=37) or GEM plus radiation (arm B; n=34), patients in arm B had greater incidence of grades 4 and 5 toxicities (41 % vs 9 %), but grades 3 and 4 toxicities combined were similar (77 % in A vs 79 % in B). No statistical differences were seen in quality of life measurements at 6, 15 to 16, and 36 weeks. The primary end point was survival, which was 9 months (95 % confidence interval 8 to 11 months) and 11 months (95 % confidence interval 8 to 16 months) for arms A and B, respectively. This trial demonstrates improved overall survival with the addition of radiation therapy to GEM in patients with localized unresectable pancreatic cancer, with acceptable toxicity [405]

A Phase II study was conducted at Indiana University to evaluate the safety and efficacy of combined weekly Gemcitabine (GEM) with external beam radiotherapy (RT) in unresectable, locally advanced pancreatic cancer (LAPC). Eligible patients had biopsy-proven LAPC without evidence of metastatic disease. In part A of the treatment plan, patients received GEM 600 mg/m² IV weekly, with concurrent RT (50.4 Gy in 28 fractions, 1.8 Gy/d, 5 days per week). Part B of the treatment plan began approximately 4 weeks after completing part A: patients without disease progression received weekly GEM 1000 mg/m² on days 1, 8, and 15 of a 28-day cycle for 6 cycles or until disease progression. From 2001 to 2003, of 28 patients evaluated, 24 (86 %) completed part A about 22 patients had grade 3 toxicities, primarily hematologic (43 %) and gastrointestinal (36 %). Three patients (11 %) had grade 4 toxicities (one each for hyperbilirubinemia, infection, and dyspnea). The median follow-up was 10 months (1-63 months) for all enrolled patients. Six patients (21 %) had a radiologic partial response, 16 (57 %) had stable disease, 5 (18 %) had progressive disease, and 1 patient (4 %) had an unevaluable response at last follow-up. Four patients (14 %) underwent surgical resection (2 with R0 resection). Median time to progression was 6 months (0-36 months). Median survival time was 10 months (95 % confidence interval 8 to 15 months). The 1- and 2-year actuarial survival rates were 30 percent and 11 percent. At last analysis, all but 2 patients died. The activity and toxicity profile of combination GEM and RT indicates that this can be safely administered for patients with LAPC [406].

5-fluorouracil (5-FU), doxorubicin, and mitomycin-C (iFAM)

In gemcitabine-pretreated pancreatic cancer, salvage chemotherapy has not been established, and the prognostic factors are not completely known. The purpose of one study was to determine the efficacy and safety of infusional 5-fluorouracil (5-FU), doxorubicin, and

mitomycin-C (iFAM) in patients with gemcitabine-pretreated pancreatic cancer and to elucidate the prognostic factors. Study eligibility was as follows: (1) 18-75 years of age; (2) relapse within 6 months after adjuvant gemcitabine-based chemotherapy (GBC) or previously treated with palliative GBC; and (3) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2. iFAM consisted of a 5-FU (800 mg/m²) infusion over 10 h on days 1-5, doxorubicin (30 mg/m²) on day 1, and mitomycin-C (8 mg/m²) on day 1 every 4 weeks. Sixty patients were enrolled. The responses to iFAM included a partial response in 6 patients (10 %) and stable disease in 8 patients (13 %). The median progression-free survival (PFS) and overall survival (OS) were 2 months (95 % confidence interval 2 to 3 months) and 6 months, respectively. The 6- and 12-month survival rates were 50 and 26 percent, respectively. Grade 3/4 hematologic toxicities included neutropenia (3 %) and thrombocytopenia (3 %). The ECOG PS was a significant prognostic factor for PFS and OS. An elevated CA 19-9 at the time of initiating iFAM was a poor prognostic factor for OS. It was concluded that iFAM is an effective and well-tolerated in patients with gemcitabine-pretreated pancreatic cancer, even patients with an ECOG PS of 2. ECOG PS and CA 19-9 were shown to be significant prognostic factors in this salvage setting [407].

S-1

The aim of this study is to investigate the prognostic value of intratumoral expression of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and orotate phosphoribosyltransferase (OPRT) in patients treated with S-1-based chemotherapy after surgical resection for pancreatic adenocarcinoma. Intratumoral TS, DPD, and OPRT expression was investigated in 106 patients with resected pancreatic adenocarcinoma by immunohistochemistry. Associations between clinicopathological factors, including intratumoral TS, DPD, and OPRT expression, and survival were evaluated by univariate and multivariate analyses. Of 106 patients, 72 had received S-1-based adjuvant chemotherapy (S-1(+) group), and 34 had not (S-1(-) group). High TS, DPD, and OPRT expression was observed in 64, 37, and 66 percent of patients, respectively. Among S-1(+) group patients, survival was significantly better for patients with low DPD expression than for patients with high DPD expression. Intratumoral DPD expression was the only independent prognostic factor for patients treated with S-1-based adjuvant chemotherapy by multivariate analysis. Intratumoral TS and OPRT expression did not appear to influence survival. Intratumoral DPD expression may be a relevant predictive marker of survival benefit associated with S-1-based adjuvant chemotherapy for pancreatic adenocarcinoma [408].

A 71-year-old male with unresectable pancreatic cancer treated with gemcitabine (GEM) by another doctor came to hospital because of stenosis of duodenum and hydronephrosis. There was peritoneal dissemination in his abdominal cavity, and gastro-jejunostomy was performed. After surgery, GEM therapy was continued until he was judged as PD. The regimen was switched to S-1/GEM combination therapy. After that, the tumor marker was down to within normal range, and abdominal symptoms improved. He is after that treated as an outpatient. S-1/GEM combination therapy is effective for patients with unresectable advanced pancreatic cancer [409].

Plus radiotherapy

S-1 is an oral fluoropyrimidine derivative that has demonstrated favorable antitumor activity in patients with metastatic pancreatic cancer. The aim of one study was to evaluate safety and efficacy of S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Patients with histopathologically proven, unresectable, locally advanced pancreatic cancer were eligible. Radiotherapy was delivered in 1.8 Gy daily fractions to a total dose of 50.4 Gy over 5.5 weeks. S-1 was administered orally twice a day at a dose of 80 mg/m²/day from day 1 to 14 and 22 to 35. Two weeks after the completion of chemoradiotherapy, maintenance chemotherapy with S-1 was administered for 28 days

every 6 weeks until progression. Thirty-four patients were enrolled in this study. The most common grade 3 toxicities during chemoradiotherapy were anorexia (24 %) and nausea (12 %). The overall response rate was 41 percent (95 % confidence interval 25 % to 58 %) and overall disease control rate (partial response plus stable disease) was 97 percent. More than 50 percent decrease in serum CA 19-9 was seen in 27 of 29 evaluable patients (93 %). The median progression-free survival was 9 months. The median overall survival and 1-year survival rate were 17 months and 71 percent, respectively. Oral S-1 and concurrent radiotherapy exerted a promising antitumor activity with acceptable toxicity in patients with locally advanced pancreatic cancer. This combination therapy seems to be an attractive alternative to conventional chemoradiotherapy using 5-fluorouracil infusion [410].

Uracil/tegafur

The objective of one study was to evaluate the efficacy and toxicity of the pre-administration of UFT (uracil/tegafur: prodrug of 5-FU) and GEM combination therapy for unresectable or recurrent pancreatic cancer in the outpatient setting. UFT (250 mg/m²/day) was orally administered from day 1 through day 6 and from day 8 through 13, and GEM (800 mg/m²/30 min) was administered on day 7 and 14, with a one-week rest every 3 weeks based on results of the previous phase I study. Thirty-six patients (24 male, 12 female) were enrolled (median age, 64 years). There were 8 partial responses (25 %). Eighteen patients (56 %) had stable disease, and 6 patients (19 %) had a progression. The median survival time was 7 months (range 2-66). Grade 3 toxicities were leucopenia (17 %), thrombocytopenia (3 %), nausea (3 %), and liver dysfunctions (3 %). There were no grade 4 toxicities. Pre-administered UFT plus gemcitabine is a promising treatment for unresectable/recurrent pancreatic cancer in the outpatient setting [411].

Salinomycin

Previous research has documented that a subpopulation of pancreatic cancer cells, named cancer stem cells (CSCs), harbor stem cell-like properties. Here, we examined the efficacy of combined treatments of salinomycin and gemcitabine in human pancreatic cancer cells. Salinomycin inhibited the growth of CSCs, while gemcitabine suppressed the viability of non-CSCs. Consistently, *in vivo* studies showed that salinomycin combined with gemcitabine could eliminate the engraftment of human pancreatic cancer more effectively than the individual agents. These data indicated that administration of salinomycin, which targets CSCs, may constitute a potential therapeutic strategy for improving the efficacy of gemcitabine to eradicate pancreatic cancer [412].

Patupilone

Patupilone is a novel microtubule-targeting cytotoxic agent with potential interaction with CYP3A4/CYP2C19 enzymes. Midazolam and omeprazole are primarily metabolized by CYP3A4 and CYP2C19, respectively. It was evaluated the inhibitory effects of patupilone on the CYP3A4/CYP2C19 pathways. One study had two parts: in an initial core phase, patients were randomly assigned to receive midazolam 4 mg or omeprazole 40 mg PO (days 1 and 29) and patupilone 10 mg/m² IV (days 8 and 29). Patients without progression continued patupilone every 3 weeks until disease progression or unacceptable toxicity (extension phase). Forty-six patients were treated. The areas under the concentration-time curves (AUC)s of midazolam with or without patupilone co-administration were similar. The C_{max} of midazolam when co-administered with patupilone was highly variable and was lower compared with midazolam alone; however, the oral clearance and terminal half-lives were similar. Both the C (max) and AUC of omeprazole when co-administered with patupilone were highly variable and lower than with omeprazole alone. However, the oral clearance and terminal half-lives were similar. The latter data suggest that patupilone decreased the

absorption of omeprazole (by ~20 %). The overall safety profile was consistent with that of previous single-agent patupilone studies; 2 partial responses (ovarian and pancreatic cancer) and 1 complete response (serous ovarian adenocarcinoma) were observed. Patupilone was not a potent CYP3A4 or CYP2C19 inhibitor. No dose adjustment is required when omeprazole or midazolam is used in patients treated with patupilone. Patupilone exhibited promising antitumor activity in heavily pretreated patients with ovarian and pancreatic cancer [413].

Cetuximab

To determine the safety of the epidermal growth factor receptor (EGFR) antibody cetuximab with concurrent gemcitabine and abdominal radiation in the treatment of patients with locally advanced adenocarcinoma of the pancreas and to evaluate the feasibility of pancreatic cancer cell epithelial-mesenchymal transition (EMT) molecular profiling as a potential predictor of response to anti-EGFR treatment. Patients with non-metastatic, locally advanced pancreatic cancer were treated in this dose escalation study with gemcitabine (0-300 mg/m²/week) given concurrently with cetuximab (400 mg/m² loading dose, 250 mg/m² weekly maintenance dose) and abdominal irradiation (50.4 Gy). Expression of E-cadherin and vimentin was assessed by immunohistochemistry in diagnostic endoscopic ultrasound fine-needle aspiration (EUS-FNA) specimens. Sixteen patients were enrolled in 4 treatment cohorts with escalating doses of gemcitabine. Incidence of grade 1-2 adverse events was 96%, and incidence of 3-4 adverse events was 9%. There were no treatment-related mortalities. Two patients who exhibited favorable treatment response underwent surgical exploration and were intraoperatively confirmed to have unresectable tumors. Median overall survival was 10.5 months. Pancreatic cancer cell expression of E-cadherin and vimentin was successfully determined in EUS-FNA specimens from 4 patients. It was concluded that cetuximab can be safely administered with abdominal radiation and concurrent gemcitabine (up to 300 mg/m²/week) in patients with locally advanced adenocarcinoma of the pancreas. This combined therapy modality exhibited limited activity. Diagnostic EUS-FNA specimens could be analyzed for molecular markers of EMT in a minority of patients with pancreatic cancer [414].

Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR). The recommended dosage is an initial load of 400 mg/m² intravenously (IV) followed by a weekly maintenance dose of 250 mg/m². It has been reported retrospectively that cetuximab efficacy was correlated with dose-related severity of skin rash. This study was prospectively designed to examine the safety and feasibility of escalating weekly doses of cetuximab, testing the hypothesis of the relationship of dose-dependent skin toxicity and efficacy. Methods Four dose levels were tested: Cetuximab 400 mg/m² IV loading dose and 250, 300, 350, 400 mg/m² weekly IV maintenance. There was no intra-patient dose escalation. Standard dose limiting toxicity criteria were used. Rash was evaluated using two additional validated dermatology methods: global acne grading scale (GAGS) and acne lesion counting (ALC). Tumor specimens and blood samples were obtained for correlative analyses. Twenty-seven patients with solid tumors were enrolled: five head and neck, three pancreas, four gall bladder, two each of prostate, breast, colorectal, lung, and esophagus, and five others. Planned dose escalation was completed without reaching dose-limiting toxicity (DLT) or the maximum tolerated dose (MTD). The highest dose level was expanded to a total of 17 patients. Gr 3/4 toxicities included: lymphopenia (n=2), fatigue (n=2), and hypomagnesemia (n=2). One patient experienced a grade 3 rash (350 mg/m²). Sixty five percent of pts had a ≥ Gr 2 rash that was not dose dependent. In 22 evaluable patients, there was one partial response (PR) in a patient with cholangiocarcinoma (400 mg/m²) and seven patients had stable disease (SD). ALC and GAGS demonstrated no correlation with dose or response. Correlative studies evaluating k-ras, EGFR FISH status and immunologic correlatives were conducted on available tumor samples. It was concluded that cetuximab

administered at 400 mg/m² IV as a loading dose with weekly maintenance dose of 400 mg/m² is feasible and well tolerated. There was no direct correlation of the grade of rash with dose in this group of patients with heterogeneous solid tumors [415].

Cetuximab, gemcitabine, and oxaliplatin

One phase II trial was designed to assess the efficacy and safety of cetuximab, gemcitabine, and oxaliplatin followed by cetuximab, capecitabine, and radiation therapy in locally advanced pancreatic cancer (LAPC). Treatment-naïve eligible patients (n=69) received intravenous gemcitabine (1,000 mg/m²) and oxaliplatin (100 mg/m²) every 2 weeks for four doses, followed by radiation (50.4 Gy to the gross tumor only) with concurrent capecitabine (825 mg/m² twice daily on radiation treatment days). Cetuximab (500 mg/m²) was started on day 1 of chemotherapy and was continued every 2 weeks during chemotherapy and chemoradiotherapy. Diagnostic cytology specimens were immunostained for Smad4(Dpc4) expression. Median overall survival time was 19 months (95 % confidence interval 14 to 24 months), and 1-year, 2-year, and 4-year actuarial overall survival rates were 66 percent, 25 percent, and 11 percent, respectively. Acneiform rash correlated with improved survival. but initial CA19-9, borderline resectable initial stage, and surgical resection (n=7) did not. The 1-year and 2-year radiographic local progression rates were 23 percent and 61 percent, respectively. The worst acute toxic effects were GI toxicity (32 % and 10 % for grades 2 and 3, respectively); fatigue (26 % and 6 % for grades 2 and 3, respectively); sensory neuropathy (9 % and 1 % for grades 2 and 3, respectively); and acneiform rash (54 % and 3 % for grades 2 and 3, respectively). Smad4(Dpc4) expression correlated with a local rather than a distant dominant pattern of disease progression. This regimen appears effective and has acceptable toxicity. The primary end point (1-year overall survival rate > 45%) was met, with encouraging survival duration. Smad4(Dpc4) immunostaining correlated with the pattern of disease progression. Prospective validation of Smad4(Dpc4) expression in cytology specimens as a predictive biomarker is warranted and may lead to personalized treatment strategies for patients with localized pancreatic cancer [416].

Capecitabine and temozolomide

Temozolomide is an active agent in metastatic pancreatic endocrine carcinomas. In vitro data indicate that the combination of capecitabine and temozolomide is synergistic for induction of apoptosis in neuroendocrine tumor cell lines. The authors retrospectively evaluated the efficacy of capecitabine and temozolomide in 30 patients with metastatic pancreatic endocrine carcinomas to assess response rate, progression free survival (PFS), and overall survival (OS). Patients with metastatic, well, or moderately differentiated pancreatic endocrine carcinomas who had not received prior systemic chemotherapy were treated with capecitabine (750 mg/m² twice daily, days 1-14) and temozolomide (200 mg/m² once daily, days 10-14) every 28 days. Among 30 patients treated, 21 (70 %) patients achieved an objective radiographic response. Median progression-free survival was 18 months. The rate of survival at two years was 92 percent . Only 4 patients (12%) experienced grade 3 or 4 adverse events. It was concluded that the combination of capecitabine and temozolomide is associated with an exceptionally high and durable response rate in metastatic endocrine carcinomas of the pancreas. Clinical endpoints, including response rate, survival, and toxicity, are superior to those observed with streptozocin-based regimens [417].

FOLFIRINOX

Data are lacking on the efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer. It was

randomly assigned 342 patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating a greater severity of illness) to receive FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at a dose of 1000 mg per square meter weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks. Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival. The median overall survival was 11 months in the FOLFIRINOX group as compared with 7 months in the gemcitabine group (hazard ratio for death, 0.57; 95 % confidence interval 0.45 to 0.73), which was a statistically significant difference. Median progression-free survival was 6 months in the FOLFIRINOX group and 3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95 % confidence interval 0.37 to 0.59). The objective response rate was 32 percent in the FOLFIRINOX group versus 9 percent in the gemcitabine group. More adverse events were noted in the FOLFIRINOX group; 5 percent of patients in this group had febrile neutropenia. At 6 months, 31 percent of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66 percent in the gemcitabine group (hazard ratio, 0.47; 95 % confidence interval 0.30 to 0.70). As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage but had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status [418].

Clinical trials in advanced pancreatic cancer during the last couple of decades have almost uniformly yielded disappointing results. To date, the paradigm for almost all phase III studies has been to compare the long-time reference standard, gemcitabine, with a gemcitabine-based combination regimen. Agents evaluated in combination with gemcitabine have been myriad; these have included both cytotoxic drugs (platinum analogs, fluoropyrimidines, and camptothecins) and targeted therapies (inhibitors of farnesyl transferase, matrix metalloproteinase, vascular endothelial growth factor, and epidermal growth factor receptor, to name a few). With the exception of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib – which produced a modest incremental improvement when added to gemcitabine – none of these individual trials demonstrated a statistically significant survival benefit in favor of doublet therapy, although some have shown improvement in secondary outcome measures such as response rate and time to tumor progression. The continued use of multidrug regimens, in fact, has been guided more by a bias in oncology practice that combination therapy is better than monotherapy, meta-analyses that indicate a survival advantage with certain combinations, particularly in patients who retain a good performance status, and practice guidelines, rather than by compelling prospective randomized phase III data. With this as background, the results of the ACCORD4/Partenariat de Recherche en Oncologie Digestive (PRODIGE) 11 trial, first presented by Conroy et al at the 2010 annual meeting of the American Society of Clinical Oncology and recently published in the May 12, 2011, issue of the *New England Journal of Medicine*, are nothing short of eye opening. In this phase II/III trial conducted at 48 centers throughout France, 342 patients with previously untreated metastatic pancreatic cancer were randomly assigned to receive either gemcitabine monotherapy or a nongemcitabine-based regimen called FOLFIRINOX (biweekly bolus plus infusional fluorouracil, leucovorin, irinotecan, and oxaliplatin). There was a statistically significant improvement for the FOLFIRINOX arm in terms of the primary end point, overall survival (median of 11 vs 7 months; hazard ratio for death 0.57). Additionally, more patients on the FOLFIRINOX arm were alive at specified landmark time points; patients on this arm demonstrated a 1-year survival rate of 48 percent compared with 21 percent on the gemcitabine arm. Other secondary end points, including median progression-free survival (6 vs 3 months) and objective response rate (32 % vs 9 %), were likewise significantly in favor of the FOLFIRINOX regimen. A median survival of close to 1 year in a purely metastatic cohort has never before been approached in any phase III study of this disease.

As such, the immediate question arises as to whether FOLFIRINOX should become the newly adopted standard of care for the front-line treatment of patients with metastatic pancreatic cancer, at least in those with preserved performance status. (Notably, patients enrolled onto this trial were required to have an Eastern Cooperative Oncology Group performance status of 0-1; there was also an upper-limit age cutoff at 76 years.) The authors offer an appropriately measured conclusion, noting in their final statement that FOLFIRINOX represents “a first-line option” (as opposed to the new gold standard) in this patient population. Not surprisingly, the FOLFIRINOX regimen was associated with higher rates of grade 3 and 4 toxicities than gemcitabine, including febrile neutropenia (5 %), diarrhea (13 %), and sensory neuropathy (9 %). The incidence of severe toxicities is of paramount concern when weighing the risks and benefits of various therapies to determine which to offer patients in a noncurative setting. Importantly, despite the aforementioned toxicities, the time to definitive quality of life (QOL) degradation (as measured by a biweekly European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) was superior in patients who received FOLFIRINOX compared with gemcitabine, presumably because of a delay in disease progression that was associated with this treatment arm. Especially in pancreatic cancer, such QOL measures are an absolutely essential component of assessing the risk/benefit ratio of any new therapeutic option, given patients' short survival duration and the pain, anorexia, and inanition that so often accompanies the underlying disease process. Although this trial was conducted exclusively in patients with metastatic pancreatic cancer, there will undoubtedly be tremendous interest in exploring FOLFIRINOX in patients with earlier stages of disease. In the setting of locally advanced unresectable pancreatic cancer, it would be appropriate to consider use of this regimen as part of induction chemotherapy, especially as one might expect a higher proportion of candidates to be fit enough to receive more aggressive chemotherapy. A number of other questions remain that may help us additionally refine our use of the FOLFIRINOX regimen. For example, are all of the individual components of FOLFIRINOX necessary, or can this combination somehow be simplified to improve tolerability without compromising efficacy? [419].

Bevacizumab

Treatment options are limited for advanced pancreatic cancer progressive after gemcitabine therapy. The vascular endothelial growth factor pathway is biologically important in pancreatic cancer, and docetaxel has modest antitumor activity. It was evaluated the role of the anti-vascular endothelial growth factor antibody bevacizumab as second-line treatment for patients with metastatic pancreatic cancer. Patients with metastatic adenocarcinoma of the pancreas who had progressive disease on a gemcitabine-containing regimen were randomized to receive bevacizumab alone or bevacizumab in combination with docetaxel. Thirty-two patients were enrolled; 16 to bevacizumab alone (Arm A) and 16 to bevacizumab plus docetaxel (Arm B). Toxicities were greater in Arm B with the most common grade 3/4 nonhematologic toxicities including fatigue, diarrhea, dehydration, and anorexia. No confirmed objective responses were observed. At 4 months, 2 of the 16 patients in Arm A and 3 of the 16 patients in Arm B were free from progression. The study was stopped according to the early stopping rule for futility. Median progression-free survival and overall survival were 43 days and 165 days in Arm A and 48 days and 125 days in Arm B. Elevated d-dimer levels and thrombin-antithrombin complexes were associated with decreased survival and increased toxicity. It was concluded that bevacizumab with or without docetaxel does not have antitumor activity in gemcitabine-refractory metastatic pancreatic cancer. Baseline and on-treatment d-dimer and thrombin-antithrombin complex levels are associated with increased toxicity and decreased survival [420].

Preclinical studies have suggested accelerated tumor growth, local invasion, and distant metastasis after withdrawal of treatment with some antiangiogenic agents. To investigate whether discontinuation of bevacizumab treatment is associated with accelerated disease progression or increased mortality, it was retrospectively analyzed five randomized, placebo-

controlled phase III studies in 4,205 patients with breast, colorectal, renal, and pancreatic cancer. Time from treatment discontinuation to progressive disease or death was analyzed in patients discontinuing bevacizumab/placebo as a result of adverse events (AEs). Mortality rates were assessed at 30, 60, 90, 120, 150, 180, and 210 days after the last bevacizumab/placebo dose in the following two groups: patients discontinuing bevacizumab/placebo as a result of AEs and patients discontinuing bevacizumab/placebo for any reason. In the same groups, time from treatment discontinuation to death was analyzed. Data on disease progression pattern were available and analyzed in four of the five studies. In the pooled analysis, median time from discontinuation as a result of AEs to progression/death was 3 months (95 % confidence interval, 3 to 4 months) for placebo and 4 months (95 % confidence interval 3 to 5 months) for bevacizumab (hazard ratio, 0.93). Mortality rates from 30 days to 210 days after treatment discontinuation and time from discontinuation to death were similar in bevacizumab- and placebo-treated patients. In addition, similar patterns of disease progression were seen in bevacizumab- and placebo-treated patients. This retrospective analysis of five placebo-controlled clinical trials does not support a decreased time to disease progression, increased mortality, or altered disease progression pattern after cessation of bevacizumab therap [421].

Gemcitabine, bevacizumab, and radiotherapy

To evaluate response rate, survival, and toxicity in patients with nonmetastatic pancreatic cancer treated with gemcitabine, bevacizumab, and radiotherapy. Patients received three cycles of therapy over 10 weeks. In total, treatment consisted of intravenous (IV) gemcitabine, 1,000 mg/m², every 1 to 2 weeks (7 doses), IV bevacizumab, 10 mg/kg every 2 weeks (5 doses), and 36 Gy of radiotherapy (2.4-Gy fractions during cycle two). Response was assessed by cross-sectional imaging and carbohydrate antigen 19-9 (CA 19-9) levels. Patients with resectable tumors underwent surgery 6 to 8 weeks after the last dose of bevacizumab. Maintenance gemcitabine and bevacizumab doses were delivered to patients who had unresected tumors and no progression. Twenty-eight of the 32 enrolled patients completed all three cycles. The median follow-up was 11.07 months. Most grade 3 or 4 toxicities occurred in the initial treatment phase; the most frequent toxicities were leukopenia (21 %), neutropenia (17 %), and nausea (17 %). At week 10, 1 patient (4 %) had a complete response, 2 patients (7 %) had partial responses, 21 patients (75 %) had stable disease, and 4 patients (14 %) had progressive disease. The median pretreatment and posttreatment CA 19-9 levels (25 patients) were 184 and 58 U/ml, respectively. One of 10 patients proceeding to surgery experienced a major complication. Two of 6 patients undergoing resection had complete pathologic responses. The median progression-free and overall survival durations were 10 months and 12 months, respectively. The combination of full-dose gemcitabine, bevacizumab, and radiotherapy was active and was not associated with a high rate of major surgical complications [422].

Erlotinib

Erlotinib combined with gemcitabine has not been evaluated in Japanese patients with unresectable pancreatic cancer. One two-step phase II study assessed the safety and pharmacokinetics of erlotinib 100 mg/day (oral) plus gemcitabine 1000 mg/m² (i.v. days 1, 8, 15) in a 28-day cycle in the first step, and efficacy and safety in the second step. The primary end-point was safety. One hundred and seven patients were enrolled (first step, n=6; second step, n=101). The most common adverse event was RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% of patients. One treatment-related death occurred. While interstitial lung disease-like events were reported in nine patients, all patients recovered or improved. The median overall survival, the 1-year survival rate and median progression-free survival were 9 months, 33 percent and 3 months, respectively. The overall response and disease

control rates were 20 percent and 50 percent, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine had acceptable toxicity and efficacy that was not inferior to that seen in Western patients [423].

2-Methoxyestradiol analog

2-methoxyestradiol (2ME2) is an estradiol-17beta metabolite with antiproliferative and antiangiogenic activities. ENMD-1198 is an analog of 2ME2 which was developed to decrease the metabolism and increase both the bioavailability and antitumor activities of the parent molecule. This first-in-human phase I study evaluated the tolerability, pharmacokinetics and preliminary evidence of activity of ENMD-1198 in advanced cancer patients. Eligible patients received ENMD-1198 orally once daily in Part A (standard 3+3 dose escalation design), or in Part B (accelerated dose escalation design). Cycle 1 consisted of 28 days daily dosing followed by a 14-(Part A) or 7-(Part B) day observation period, then continuously in 28 day cycles thereafter. A total of 29 patients were enrolled in 12 dose cohorts (5 to 550 mg/m²/d). The most common drug-related toxicities were Grade 1/2 fatigue (55 %), nausea and vomiting (37 %), and constipation (34 %). Two DLTs (grade 4 neutropenia) occurred at 550 mg/m²/day, and 425 mg/m²/d was declared the maximum tolerated dose. ENMD-1198 was absorbed rapidly with a T(max) of 1-2 h. Exposure to ENMD-1198 (C_{max} and AUC₀₋₂₄ hr increased linearly with dose. The mean terminal half-life was 15 h. A 3-fold accumulation was found after multiple doses. Five patients achieved stabilization of disease for at least 2 cycles, three of whom (with neuroendocrine carcinoma of pancreas, prostate cancer and ovarian cancer) demonstrated prolonged stabilization ranging from 8-24.5 cycles. It was concluded that ENMD-1198 is well-tolerated with a pharmacokinetic exposure profile compatible with once daily dosing. The recommended phase II dose of ENMD-1198 is 425 mg/m²/d. Early evidence of prolonged disease stabilization in pre-treated patients suggests ENMD-1198 is worthy of additional investigation [424].

Phase 1 studies

The outcomes of patients with pancreatic cancer treated on early phase clinical trials have not been systematically analyzed. The purpose of one study was to report the presenting characteristics and outcomes of patients with locally advanced or metastatic pancreatic cancer treated on phase 1 clinical trials at a single institution. The authors reviewed the records of consecutive patients with metastatic pancreatic cancer who were treated in the phase I Clinical Trials Program at The University of Texas M. D. Anderson Cancer Center from 2004 to 2009. Data recorded and analyzed included survival, response, and disease characteristics. Eighty-three patients were identified. The median age was 62 years (range, 39-81 years). Of 78 patients evaluable for response, 2 (3 %) had a partial response (PR), and 10 (13 %) had stable disease (SD) for ≥ 4 months. With a median follow-up for survivors of 4 months, the median survival from presentation in the phase 1 clinic was 5 months (95 % confidence interval 3 to 6). The median overall survival from diagnosis was 22 months (95 % confidence interval 18 to 27). The median time to treatment failure was 2 months (95 % confidence interval 1 to 2). Independent factors associated with lower rates of PR/SD were liver metastases and performance status >0. Independent factors associated with shorter survival were liver metastases, low calcium level, and elevated CEA level (>6 ng/mL). The results suggest that phase 1 clinical trials offer a reasonable therapeutic approach for patients with advanced pancreatic cancer [425].

Liposome based delivery systems

Despite rapid advances in cancer diagnosis and treatment, pancreatic cancer remains one of the most difficult human malignancies to be treated, with a mortality rate nearly equal to its

incidence. Although gemcitabine has been established as the standard first-line treatment for advanced pancreatic cancer, gemcitabine-based combination chemotherapy showed either marginal or no improvement in survival. Developments in liposomal delivery systems have facilitated the targeting of specific agents for cancer treatment. Such systems could be developed as platforms for future multi-functional theranostic nanodevices tailor-made for the combined detection of early cancer and functional drug delivery. It was systemically reviewed liposome based drug-delivery systems, which can provide improved pharmacokinetics, reduced side effects and potentially increased tumor uptake, for pancreatic cancer therapy. Novel liposomal formulations allowing for higher tumor targeting efficiencies and used in current clinical trials to treat this challenging disease are emphasized [426].

Side effects of cytostatics for pancreatic cancer

The incidence of pancreatic or biliary tract cancer is increasing in our aging population, but little is known of treatment outcomes in elderly patients with pancreatic or biliary tract cancer. Patients with pancreatic or biliary tract cancer who received chemotherapy between 2007 and 2009 were retrospectively reviewed to compare treatment outcomes between the elderly (aged 75 years or older) and the younger patients. Data were collected of patient backgrounds, adverse events and dose intensity within the first two cycles and overall survival time. Of the 102 who met the inclusion criteria, 19 were elderly who were introduced to full dose chemotherapy. Medication for their comorbidities was required in 15 (79 %) of the 19 elderly patients and in 27 (33%) of 83 younger patients. The frequencies of haematological adverse events of grades 3 or 4 were 42 percent and 39 percent, and those of non-haematological adverse events were 21 percent and 16 percent, for the elderly and younger, respectively. Similar dose intensities were delivered to the elderly and younger. Also, similar proportions of elderly and younger received dose reductions. There was no difference in overall survival between the elderly and the younger. No clear difference in treatment outcomes was seen between the elderly and the younger patients who received gemcitabine alone. Gemcitabine chemotherapy appears to be safe and the same treatment effect was seen even in older patients with pancreatic or biliary tract cancer [427].

Isoflavones

The EGFR/Akt/NF-kappaB signalling pathway is frequently deregulated in pancreatic cancer and contributes to cell growth, metastasis and chemoresistance. An isoflavone, genistein, inactivates Akt and NF-kappaB and enhances the anti-tumor activity of erlotinib and gemcitabine in experimental systems of pancreas cancer. This phase II study was undertaken to determine the effects of adding isoflavone to a regimen of gemcitabine and erlotinib on survival in patients with advanced pancreatic cancer. Eligibility included previously untreated patients with advanced pancreatic adenocarcinoma. Patients received gemcitabine 1,000 mg/m² on days 1, 8, and 15, and erlotinib 150 mg once daily peroral. on day 1 to day 28. Soy isoflavones (Novasoy®) were administered at a dose of 531 mg twice daily peroral starting day -7 until the end of study participation. Twenty patients with advanced pancreas cancer were enrolled (median age 56 years). Sixteen patients had stage IV disease. The median number of cycles was 2 per patient. The median survival time was 5 months (95 % confidence interval 4.6 to N/A months). The probability of survival at 6 months was 50 percent (95 % confidence interval 32 to 78 %). It was concluded that the addition of soy isoflavones to gemcitabine and erlotinib did not appear to increase the survival of patients with advanced pancreatic cancer [428].

New modalities

Pancreatic cancer cells with defects in the BRCA2-PALB2-Fanconi DNA repair pathway are sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors. PARP enzymes add large

branched chains of poly (ADP-ribose) on nicked DNA, which cause separation of histones from DNA, to enable DNA repair. In phase 1/2 clinical trials of patients with a germline BRCA2 gene mutation, response rates of about 40 percent were recorded with olaparib for recurrent breast and ovarian cancer. Clinical trials of PARP inhibitors for patients with pancreatic cancer are currently underway. The hedgehog pathway inhibitor GDC-0449 (Genentech, San Francisco, CA, USA) is under investigation in a phase 2 clinical trial, in combination with gemcitabine and the nanoparticle formulation of paclitaxel, in patients with metastatic pancreatic adenocarcinoma (NCT01088815). Other therapeutic agents being studied include the multikinase inhibitor, sorafenib, and agents targeting SRC (dasatinib), gamma-secretase, MTOR, TNFSF10 (also known as TRAIL), and IGF1. Endoscopic treatments are under investigation for pancreatic cancer, including endoscopic delivery of chemotherapy, cryotherapy, photodynamic therapy, and radiofrequency ablation, but no evidence exists that these agents are as effective as standard treatment [213].

Noscapine analogues

Microtubules, composed of alpha/beta tubulin heterodimers, represent a validated target for cancer chemotherapy. Thus, tubulin- and microtubule-binding antimitotic drugs such as taxanes and vincas are widely employed for the chemotherapeutic management of various malignancies. Although quite successful in the clinic, these drugs are associated with severe toxicity and drug resistance problems. Noscapinoids represent an emerging class of microtubule-modulating anticancer agents based upon the parent molecule noscapine, a naturally occurring non-toxic cough-suppressant opium alkaloid. Here we report in silico molecular modeling, chemical synthesis and biological evaluation of novel analogs derived by modification at position-7 of the benzofuranone ring system of noscapine. The synthesized analogs were evaluated for their tubulin polymerization activity and their biological activity was examined by their antiproliferative potential using representative cancer cell lines from varying tissue-origin [A549 (lung), CEM (lymphoma), MIA PaCa-2 (pancreatic), MCF-7 (breast) and PC-3 (prostate)]. Cell-cycle studies were performed to explore their ability to halt the cell-cycle and induce subsequent apoptosis. The varying biological activity of these analogs that differ in the nature and bulk of substituent at position-7 was rationalized utilizing predictive in silico molecular modeling [429].

Predicting chemosensitivity

Gemcitabine (GEM) is the standard treatment for advanced/metastatic pancreatic cancer. However, there is a substantial subset of patients in whom the efficacy of GEM, when used as a single agent, is inadequate. Recently, the 5-fluorouracil (5-FU) prodrugs capecitabine and S-1 have been used as an alternative, either alone or in combination with GEM. The aim of the one study was to investigate the expression pattern of genes that render pancreatic cancer cells sensitive to GEM and 5-FU, and to identify markers for individualized chemotherapy, even in patients who have developed resistance. It was investigated the correlation between the expression of genes associated with the metabolism of GEM and 5-FU, and sensitivity to these drugs in 15 human pancreatic cancer cell lines. It was also established GEM- and 5-FU-resistant pancreatic cancer cell lines to investigate changes in the expression levels of these genes and the effects of one drug on cells resistant to the other. We found no correlation between pancreatic cancer cell sensitivity to either GEM- or 5-FU. GEM-resistant cells did not become resistant to 5-FU and vice versa. High expression of RRM1 and TS x DPD correlated significantly with sensitivity to GEM and 5-FU, respectively. 5-FU-resistant cells expressed significantly higher levels of TP than parental cells. In conclusion, pancreatic cancer cells showed no cross-resistance to GEM and 5-FU. Quantitative analyses of RRM1, TP, DPD and TS mRNA levels in pancreatic cancer cells may be useful for predicting their sensitivity to GEM and 5-FU [430].

Drug resistance

The current standard care for metastatic pancreatic cancer is gemcitabine, however, the success of this treatment is poor and overall survival has not improved for decades. Drug resistance (both intrinsic and acquired) is thought to be a major reason for the limited benefit of most pancreatic cancer therapies. Previous studies have indicated various mechanisms of drug resistance in pancreatic cancer, including changes in individual genes or signaling pathways, the influence of the tumor microenvironment, and the presence of highly resistant stem cells. One review summarized recent advances in the mechanisms of drug resistance in pancreatic cancer and potential strategies to overcome this. Increasing drug delivery efficiency and decreasing drug resistance is the current aim in pancreatic cancer treatment, and will also benefit the treatment of other cancers. Understanding the molecular and cellular basis of drug resistance in pancreatic cancer will lead to the development of novel therapeutic strategies with the potential to sensitize pancreatic cancer to chemotherapy, and to increase the efficacy of current treatments in a wide variety of human cancers [431].

High-intensity focused ultrasound (HIFU)

The aim of one study was to evaluate safety and efficacy of high-intensity focused ultrasound (HIFU) for advanced pancreatic cancer (PC). Patients with PC TNM stage III or IV were included. Magnetic resonance imaging was performed 2 weeks before and after the HIFU. The ablating tumor volume was calculated by ratio of the nonperfused necrotic area of the planned area on contrast-enhanced T1-weighted image on post-HIFU magnetic resonance imaging. The ablation results were stratified into 4 ranges: 100 to 90 percent unenhanced area of targeting area, 90 to 50 percent, within 50 percent, and no change. High-intensity focused ultrasound treatment was performed without severe adverse event in 46 patients, 49 times (male-female = 25:21; mean age, 61 ± 10; TNM stage 3-stage 4 = 18:28). Average size of the PC lesion was 4 ± 1 cm (2-9 cm). After HIFU treatment, ablating tumor volume was as follows: 90 to 100 percent in 38 lesions, 90 to 50 percent in 8, and within 50 percent in 3. Overall median survival (S1) from initial PC diagnosis was 12 months. Overall survival (S2) rates at 6, 12, and 18 months from HIFU were 52 percent, 30 percent, and 22 percent, respectively, with a median survival of 7 months. High-intensity focused ultrasound is safe and effective, which induced excellent local tumor control in most patients with advanced PC [432].

The purpose of one study was to evaluate the safety and efficacy of ultrasound-guided high-intensity focused ultrasound (USgHIFU) for ablation of solid tumours without damaging the surrounding structures. A specific written informed consent was obtained from every patient before treatment. From 2008 to 2009, 22 patients with 29 lesions were treated: nine patients with liver and/or soft-tissue metastases from colorectal carcinoma (CRC), six with pancreatic solid lesions, three with liver and/or bone metastases from breast cancer, one with osteosarcoma, one with muscle metastasis from lung cancer, one with iliac metastasis from multiple myeloma and one with abdominal liposarcoma. The mean diameter of tumours was 4.2 cm. All patients were evaluated 1 day, 1 month and 3 months after HIFU treatment by multidetector computed tomography (MDCT), positron-emission tomography (PET)-CT and clinical evaluation. The treatment time and adverse events were recorded. All patients had one treatment. Average treatment and sonication times were, respectively, 163 and 37 min. PET-CT or/and MDCT showed complete response in 11/13 liver metastases; all bone, soft-tissue and pancreatic lesions were palliated in symptoms, with complete response to PET-CT, MDCT or magnetic resonance imaging (MRI); the liposarcoma was almost completely ablated at MRI. Local oedema was observed in three patients. No other side effects were observed. All patients were discharged 1-3 days after treatment. It was concluded that according to this preliminary experience in a small number of patients, it was conclude that

HIFU ablation is a safe and feasible technique for locoregional treatment and is effective in pain control [433].

Vaccine

Dendritic cell (DC)-based vaccination can induce antitumor T cell responses in vivo. One clinical pilot study examined feasibility and outcome of DC-based tumor vaccination for patients with advanced pancreatic adenocarcinoma. Tumor lysate of patients with pancreatic carcinoma was generated by repeated freeze-thaw cycles of surgically obtained tissue specimens. Patients were eligible for DC vaccination after recurrence of pancreatic carcinoma or in a primarily palliative situation. DC were generated from peripheral blood mononuclear cells (PBMC), loaded with autologous tumor lysate, stimulated with TNF-alpha and PGE₂ and injected intradermally. All patients received concomitant chemotherapy with gemcitabine. Disease response was the primary endpoint. Individual immunological responses to DC vaccination were analyzed by T cell-based immunoassays using pre- and post-vaccination samples of non-adherent PBMC. Twelve patients received DC vaccination and concomitant chemotherapy. One patient developed a partial remission, and two patients remained in stable disease. Median survival was 11 months. No severe side effects were observed. Tumor-reactive T cells could be detected prior to vaccination. DC vaccination increased the frequency of tumor-reactive cells in all patients tested; however, the degree of this increase varied. To quantify the presence of tumor-reactive T cells, stimulatory indices (SI) were calculated as the ratio of proliferation-inducing capacity of lysate-loaded versus -unloaded DC. The patient with longest overall survival of 56 months had a high SI of 6.49, indicating that the presence of a pre-vaccination antitumor T cell response might be associated with prolonged survival. Five patients survived 1 year or more. It was concluded that DC-based vaccination can stimulate an antitumoral T cell response in patients with advanced or recurrent pancreatic carcinoma receiving concomitant gemcitabine treatment [434].

K-ras mutations are frequently found in adenocarcinomas of the pancreas and can elicit mutation-specific immune responses. Targeting the immune system against mutant Ras may thus influence the clinical course of the disease. Twenty-three patients who were vaccinated after surgical resection for pancreatic adenocarcinoma (22 pancreaticoduodenectomies, one distal resection), in two previous Phase I/II clinical trials, were followed for more than 10 years with respect to long-term immunological T-cell reactivity and survival. The vaccine was composed of long synthetic mutant ras peptides designed mainly to elicit T-helper responses. Seventeen of 20 evaluable patients (85 %) responded immunologically to the vaccine. Median survival for all patients was 28 months and 28 months for immune responders. The 5-year survival was 22 percent and 29 percent, respectively. Strikingly, 10-year survival was 20 percent (four patients out of 20 evaluable) versus zero (0/87) in a cohort of nonvaccinated patient treated in the same period. Three patients mounted a memory response up to 9 years after vaccination. The present observation of long-term immune response together with 10-year survival following surgical resection indicates that K-ras vaccination may consolidate the effect of surgery and represent an adjuvant treatment option for the future [435].

Side effects

The purpose of one study was to investigate severe adverse events (SAEs) after therapeutic peptide vaccination for advanced cancer patients. It was investigated SAEs following personalized peptide vaccinations in 500 advanced cancer patients, including 174 prostate, 74 colon, 51 pancreatic and 43 gastric cancer patients. The number of vaccination cycles varied widely, from 3 to 112. The severity of adverse events was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3, and events with a grade of >3 were defined as SAEs and were evaluated by the Institutional

Safety Evaluation Committee. A total of 215 SAEs in 102 patients were recorded during the vaccine trials. The main causes for these events were cancer progression (152 SAEs in 78 patients), combined cancer treatments other than vaccination (35 in 21 patients), diseases other than cancer (20 in 19 patients), peptide vaccines (6 in 6 patients) and suicide (1 in 1 patient). The 6 vaccine-related SAEs, all grade 3, consisted of skin reactions at each injection site, cellulitis around the injection site, edemas of the head and neck regions, colitis, rectal bleeding and bladder-vaginal fistulae. Both cellular and humoral responses to the vaccinated peptides were highly boosted in all 6 of these patients, indicating the involvement of augmented immune responses in these SAEs. The clinical responses in these 6 patients consisted of 2 partial responses and 4 stable diseases. The majority of SAEs after peptide vaccination for advanced cancer patients were caused by cancer progression. The appearance of vaccine-related SAEs, except inflammatory injection site reactions, was unexpected, and fortunately the incidence was very low. The results suggest that physicians should be on guard for these rare SAEs associated with augmented immune responses [436].

Curcumine

Curcumin (CUR) is an active food compound, but its insolubility and instability in water contributes to low bioavailability. In this study, the solubility of CUR was enhanced by utilizing the solubilizing properties of rubusoside (RUB). The solubility of CUR in water increased linearly from 61 µg/mL to 2.318 mg/mL in the presence of RUB ranging from 1 to 10 percent (w/v). Dynamic light scattering and transmission electron microscopy studies found that CUR and RUB formed CUR-RUB nanoparticle (about 8 nm) complexes. The RUB-solubilized CUR was stable in physiological conditions and did not precipitate when diluted or degrade when spray-dried to a completely reconstitutable powder. Furthermore, cell viability assays demonstrated the efficacy of RUB-solubilized CUR against human colon, breast, and pancreatic cancer cell lines. The development of this new solubilized, stable, and biologically active CUR formulation lays the foundation for future bioavailability improvement [437].

Curcumine plus gemcitabine

Curcumin, a plant-derived natural polyphenol, could be a promising anti-cancer drug and shows synergic effects with cytotoxic agents. It was evaluated the safety and feasibility of combination therapy using curcumin with gemcitabine-based chemotherapy. Gemcitabine-resistant patients with pancreatic cancer received 8 g oral curcumin daily in combination with gemcitabine-based chemotherapy. The primary endpoint was safety for phase I and feasibility of oral curcumin for phase II study. Twenty-one patients were enrolled. No dose-limiting toxicities were observed in the phase I study and oral curcumin 8 g/day was selected as the recommended dose for the phase II study. No patients were withdrawn from the study because of the intolerability of curcumin, which met the primary endpoint of the phase II study, and the median compliance rate of oral curcumin was 100 percent (range 79-100 %). Median survival time after initiation of curcumin was 161 days (95 % confidence interval 109 to 223 days) and 1-year survival rate was 19 percent. Plasma curcumin levels ranged from 29 to 412 ng/ml in five patients tested. It was concluded that combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with pancreatic cancer and warrants further investigation into its efficacy [438].

Experimental

Ultraviolet light

Although gemcitabine is recognized as the standard drug for the treatment of advanced pancreatic cancer, the clinical outcome is not satisfactory. It was recently reported that relatively high dose ultraviolet-C (UV-C; 200J) inhibits cell growth by desensitization of epidermal growth factor receptor (EGFR) in human pancreatic cancer cells. In the present

study, we investigated the combination effects of low dose UV-C (10J) and gemcitabine on apoptosis and cell growth in these cells. UV-C enhanced gemcitabine-induced suppression of cell viability. In addition, the combination use clearly induced apoptosis, while neither UV-C nor gemcitabine alone did. Concurrently, combination use caused the decrease in the EGFR protein level and reduced EGF-induced activation of Akt pathway, subsequently resulting in accumulation of beta-catenin. The order of the treatment with UV-C and gemcitabine did not affect their synergistic effects on apoptosis and cell growth. Interestingly, combination use synergistically induced phosphorylation of 5' AMP-activated protein kinase (AMPK) alpha at Thr172 and acetyl-CoA carboxylase at Ser79 as a downstream molecular target of AMPK. AMPK activator, 5-aminoimidazole-4-carboxamide-1-beta-ribose, induced apoptosis and suppressed cell growth in these cells, thus suggesting that combination effects of UV-C and gemcitabine is due to the activation of AMPK. Together, the findings could provide a new aspect of pancreatic cancer therapy [439].

Radiotherapy

Stereotactic body radiotherapy (SBRT) has been used successfully to treat patients with locally advanced pancreas cancer. However, many patients develop metastatic disease soon after diagnosis and may receive little benefit from such therapy. It was therefore retrospectively analyzed a planned strategy of initial chemotherapy with restaging and then treatment for those patients with no evidence of metastatic progression with SBRT. Forty-seven patients received gemcitabine (1,000 mg/m² per week for 3 weeks then 1 week off) until tolerance, at least six cycles, or progression. Patients without metastases after two cycles were treated with SBRT (tolerance-based dose of 24-36 Gy in 3 fractions) between the third and fourth cycles without interrupting the chemotherapy cycles. Eight of the 47 patients (17 %) were found to have metastatic disease after two cycles of gemcitabine; the remaining 39 patients received SBRT. The median follow-up for survivors was 21 months (range, 6-36 months). The median overall survival for all patients who received SBRT was 20 months, and the median progression-free survival was 15 months. The local control rate was 85 percent (33 of 39 patients); and 54 percent of patients (21 of 39) developed metastases. Late Grade III toxicities such as GI bleeding and obstruction were observed in 9 percent (3/39) of patients. It was concluded that for patients with locally advanced pancreas cancer, this strategy uses local therapy for those who are most likely to benefit from it and spares those patients with early metastatic progression from treatment. SBRT delivers such local therapy safely with minimal interruption to systemic chemotherapy, thereby potentially improving the outcome in these patients [440].

To evaluate the current status of stereotactic body radiotherapy (SBRT) and identify both advantages and disadvantages of its use in developing countries, a meeting composed of consultants of the International Atomic Energy Agency was held in Vienna in November 2006. Owing to continuous developments in the field, the meeting was extended by subsequent discussions and correspondence (2007-2010), which led to the summary presented here. The advantages and disadvantages of SBRT expected to be encountered in developing countries were identified. The definitions, typical treatment courses, and clinical results were presented. Thereafter, minimal methodology/technology requirements for SBRT were evaluated. Finally, characteristics of SBRT for developing countries were recommended. Patients for SBRT should be carefully selected, because single high-dose radiotherapy may cause serious complications in some serial organs at risk. Clinical experiences have been reported in some populations of lung cancer, lung oligometastases, liver cancer, pancreas cancer, and kidney cancer. Despite the disadvantages expected to be experienced in developing countries, SBRT using fewer fractions may be useful in selected patients with various extracranial cancers with favorable outcome and low toxicity [441].

The aim of one study was to assess the feasibility and safety of stereotactic body radiotherapy (SBRT) in patients with advanced pancreatic adenocarcinoma. It was reviewed outcomes of 71 patients treated with SBRT for pancreatic cancer between 2004 and 2009. Forty patients (56 %) had locally unresectable disease, 11 patients (16 %) had local recurrence following surgical resection, 8 patients (11 %) had metastatic disease, and 12 patients (17 %) received adjuvant SBRT for positive margins. The median dose was 24 Gy (18-25 Gy), given in a single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meier survival analyses were used to estimate freedom from local progression (FFLP) and overall survival (OS) rates. The median follow-up among surviving patients was 13 months (4-26 months). The median tumor volume was 17 mL (5-249 mL). The overall FFLP rates at 6 months/1 year were 72 and 49 percent, respectively. Among those with macroscopic disease, FFLP was achieved in 77 percent of patients with tumor size <15 mL (n=22), and 60 percent for ≥15 mL (n=37). FFLP was achieved in 73 percent following 24 to 25 Gy, and 45 percent with 18 to 22 Gy. The median OS was 10 months, with 6 month/1 year OS rates of 65 and 41 percent, respectively. Grade 1-2 acute and late GI toxicity were seen in 40 percent of patients. Three patients experienced acute grade 3 toxicities. SBRT is feasible, with minimal grade ≥3 toxicity. The overall FFLP rate for all patients was 65 percent, comparable to rates with external beam radiotherapy. This shorter treatment course can be delivered without delay in adjuvant systemic therapy [442].

To study the impact of the 4DCT imaging technique on radiotherapy planning for pancreatic carcinoma and contrast-enhanced 4DCT scans of 15 patients (PTs) with unresectable pancreatic cancer were acquired. A 4DCT based PTV (4D-PTV) was created by the convolution of contours and then expanded for geometric uncertainties; a standard PTV (STD-PTV) was derived from a single CTV plus conventional margins. Two 3D conformal treatment (3DCRT) plans and one Helical Tomotherapy (HT) plan were generated with a prescription of 60 Gy. Regarding the 3DCRT plans, the 4D-PTV was considered as the target volume for one, and the STD-PTV for the other; the HT plans were performed only for 4D-PTV. Twelve of 15 PTs were admitted to a Phase I hypofractionated study (15 fractions). The prescribed dose was 44.25 Gy to the 4D-PTV and the PTV subvolume around vascular involvement was boosted from 50 to 55 Gy; before treatment, daily patient position was corrected using MVCT. 4D-PTVs were smaller than STD-PTVs with a volume reduction equal to 37%. 3DCRT plans on 4D-PTV showed a significant sparing of most OARs, the use of IMRT allowed a further significant dose reduction. In the Phase I study the PTV subvolume received up to 55 Gy with modest increase in dose to OARs. It was concluded that the 4DCT procedure decreases the overlap between PTV and OARs. HT technique, compared with 3DCRT, allows efficient dose sparing in particular for the duodenum. The IMRT/IGRT approach allows a safe dose escalation to PTV subvolume [443].

The 5-year overall survival of patients with pancreatic cancer is approximately 5 percent, with potentially resectable disease representing the curable minority. Although surgical resection remains the cornerstone of treatment, local and distant failure rates are high after complete resection, and debate continues as to the appropriate adjuvant therapy. Many oncologists advocate for adjuvant chemotherapy alone, given that high rates of systemic metastases are the primary cause of patient mortality. Others, however, view locoregional failure as a significant contributor to morbidity and mortality, thereby justifying the use of adjuvant chemoradiation. As in other gastrointestinal malignancies, neoadjuvant chemoradiotherapy offers potential advantages in resectable patients, and clinical investigation of this approach has shown promising results; however, phase III data are lacking. Further therapeutic advances and prospective trials are needed to better define the optimal role of adjuvant and neoadjuvant treatment in patients with resectable pancreatic cancer [444].

Intensity-modulated radiation therapy

Among patients with upper abdominal malignancies, intensity-modulated radiation therapy (IMRT) can improve dose distributions to critical dose-limiting structures near the target. Whether these improved dose distributions are associated with decreased toxicity when compared with conventional three-dimensional treatment remains a subject of investigation. Forty-six patients with pancreatic/ampullary cancer were treated with concurrent chemoradiation (CRT) using inverse-planned IMRT. All patients received CRT based on 5-fluorouracil in a schema similar to Radiation Therapy Oncology Group (RTOG) 97-04. Rates of acute gastrointestinal (GI) toxicity for this series of IMRT-treated patients were compared with those from RTOG 97-04, where all patients were treated with three-dimensional conformal techniques. The overall incidence of Grade 3-4 acute GI toxicity was low in patients receiving IMRT-based CRT. When compared with patients who had three-dimensional treatment planning (RTOG 97-04), IMRT significantly reduced the incidence of Grade 3-4 nausea and vomiting (0 % vs 11 %) and diarrhea (3 % vs 18 %). There was no significant difference in the incidence of Grade 3-4 weight loss between the two groups of patients. IMRT is associated with a statistically significant decrease in acute upper and lower GI toxicity among patients treated with CRT for pancreatic/ampullary cancers. Future clinical trials plan to incorporate the use of IMRT, given that it remains a subject of active investigation [445].

Intraoperative radiotherapy

To retrospectively analyze the results of intraoperative radiotherapy (IORT) + external beam radiotherapy (EBRT) for unresectable pancreatic cancer the records of 144 patients treated with IORT, with or without, EBRT were reviewed. One hundred and thirteen patients (79 %) were treated with IORT + EBRT and 114 patients (79 %) were treated in conjunction with chemotherapy. The median doses of IORT and EBRT were 25 Gy and 45 Gy, respectively. The median follow-up of all 144 patients was 10 months (range, ½-70 months). At the time of this analysis, 131 of 144 patients (91 %) had disease recurrences. Local progression was observed in 60 patients (42 %), and the 2-year local control rate in all patients was 45 percent. Patients treated with IORT, with or without, EBRT had significantly more favorable local control (2-year LC, 51 %) than those treated with IORT without EBRT. The 2-year overall survival (OS) rate and the median survival time in all 144 patients were 15 percent and 11 months, respectively. Patients treated with chemotherapy had a significantly favorable OS than those treated without chemotherapy. On univariate analysis, chemotherapy use alone had a significant impact on OS and on multivariate analysis; chemotherapy use was a significant prognostic factor. Late gastrointestinal morbidity of National Cancer Institute-Common Terminology Criteria grade 3 was observed in 2 patients (1%). It was concluded that IORT + EBRT yields a relatively favorable local control rate for unresectable pancreatic cancer with low frequency of severe late toxicity, and IORT combined with chemotherapy conferred a survival benefit compared with IORT without chemotherapy [446].

To assess the prognostic effect of intraoperative radiotherapy (IORT) in unresectable pancreatic cancer it was reviewed 198 patients with unresectable pancreatic cancer, which was found during experimental laparotomy. Liver metastasis was observed in 70 patients, peritoneal metastasis in 44, liver and peritoneal metastasis in 23 and locally advanced tumor in 61. Treatment consisted of IORT with or without postoperative chemotherapy. Overall survival (OS) and prognostic factors were evaluated for each pattern of disease spread. IORT was performed in 120 patients, and chemotherapy was administered in 80. Sixty patients did not receive either treatment. OS in the untreated group was significantly inferior to that for IORT alone and IORT plus gemcitabine (GEM)-based chemotherapy. IORT and GEM-based chemotherapy were identified as independent prognostic factors (hazard ratio

and 0.43). IORT was an independent prognostic determinant for patients with peritoneal metastasis (HR 0.24) but not for those with liver metastasis (HR 0.78). The authors concluded that IORT followed by GEM-based chemotherapy is the recommended treatment strategy in unresectable pancreatic cancer [447].

External radiotherapy

When treating pancreatic cancer using standard (ST) 3D conformal radiotherapy (3D-CRT) beam arrangements, the kidneys often receive a higher dose than their probable tolerance limit. Our aim was to elaborate a new planning method that – similarly to IMRT – effectively spares the kidneys without compromising the target coverage. Conformal kidneys sparing (CONKISS) 5-field, noncoplanar plans were compared with ST plans for 23 consecutive patients retrospectively. Optimal beam arrangements were used consisting of a left- and right-wedged beam-pair and an anteroposterior beam inclined in the caudal direction. The wedge direction determination (WEDDE) algorithm was developed to adjust the adequate direction of wedges. The aimed organs at risk (OARs) mean dose limits were: kidney <12 Gy, liver <25 Gy, small bowels <30 Gy, and spinal cord maximum <45 Gy. Conformity and homogeneity indexes with z-test were used to evaluate and compare the different planning approaches. The mean dose to the kidneys decreased significantly: left kidney 7.7 vs. 10.7 Gy, right kidney 9.1 vs. 11.7 Gy. Meanwhile the mean dose to the liver increased significantly (18.1 vs. 15.0 Gy). The changes in the conformity, homogeneity, and in the doses to other OARs were not significant. The CONKISS method balances the load among the OARs and significantly reduces the dose to the kidneys, without any significant change in the conformity and homogeneity. Using 3D-CRT the CONKISS method can be a smart alternative to IMRT to enhance the possibility of dose escalation [448].

Regional hyperthermia

A study was done to evaluate the therapeutic effect of delivering regional hyperthermia (HT) plus chemoradiotherapy (CRT) in patients suffering from locally advanced unresectable pancreatic cancer (LAPC). Between 2000 and 2008, 68 patients affected by primary (56/68) or recurrent (12/68) LAPC were treated either with CRT alone or CRT plus HT. Radiotherapy (RT) consisted of 3D conformal irradiation of tumor and regional lymph nodes (dose ranged from 30 Gy/10 fractions to 66 Gy/33 fractions). Chemotherapy (CT) consisted of gemcitabine (GEM) alone or in association with either oxaliplatin, or cisplatin, or 5-FU. HT was delivered twice a week, concomitant with RT. In the current study, 60 of the original 68 patients were included. Median overall survival (OS) was 15 months in the HT group versus 11 months in the control group. HT did not increase CRT toxicity. HT can be added safely to CRT in LAPC, thus, resulting in slightly prolonged survival in certain cases [449].

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Intraductal papillary mucinous neoplasms harbor many of the genetic alterations recorded in pancreatic intraepithelial neoplasias but with notable differences – e.g. intraductal papillary mucinous neoplasms rarely inactivate SMAD4 [397]:

- Intraductal papillary mucinous neoplasms can affect pancreatic branch ducts, main ducts, or both
- Most small asymptomatic intraductal papillary mucinous neoplasms in branch ducts have low malignant potential, so international guidelines have been developed for their management

- If the patient can tolerate surgery, resection of intraductal papillary mucinous neoplasms should be done if the neoplasm is in the main pancreatic duct, if it is associated with symptoms, if it is larger than 3 cm, and if it has a mural nodule
- By contrast, most intraductal papillary mucinous neoplasms confined to branches of the main pancreatic duct (branch-duct neoplasms) have low malignant potential but should be followed up with regular pancreatic imaging, with the imaging interval based primarily on lesion size
- Branch-duct intraductal papillary mucinous neoplasms of 1-3 cm in size should be assessed by endoscopic ultrasound and magnetic resonance cholangiopancreatography
- CT is also appropriate for intraductal papillary mucinous neoplasms, but since many patients need repeated imaging, some prefer alternate MRI and endoscopic ultrasound, thereby avoiding repeated radiation associated with CT
- Surgical resection is recommended for intraductal papillary mucinous neoplasms if high-risk stigmata are present
- Criteria for surveillance and resection could be different for patients with a strong family history of pancreatic cancer because they typically have concurrent microscopic PanIN that cannot be followed up accurately by imaging
- A less frequent precursor to pancreatic cancer is the mucinous cystic neoplasm, which is composed of mucin-producing epithelial cells and an associated ovarian-type stroma
- Unlike intraductal papillary mucinous neoplasms, mucinous cystic neoplasms do not communicate with pancreatic ducts
- Mucinous cystic neoplasms arise predominantly in women; about a third of these neoplastic precursors have an associated invasive carcinoma

The purpose of one study was to characterize the clinicopathological features of invasive carcinomas arising in intraductal papillary mucinous neoplasms of the pancreas (IPMN) by histological subtype of the invasive component and to compare the outcomes of these patients to a cohort of matched patients with conventional ductal pancreatic adenocarcinoma. Two distinct histological subtypes of invasive carcinomas arising in IPMNs have been described, colloid carcinoma and tubular carcinoma. Previous reports have suggested prognostic differences between these two subtypes but a matched comparison of colloid carcinoma, tubular carcinoma, and conventional pancreatic adenocarcinoma has not been reported. The clinicopathological variables of 59 patients resected for an invasive component of IPMN were analyzed with detailed pathologic review of histopathologic subtype (colloid carcinoma and tubular carcinoma). Using a postresection pancreatic adenocarcinoma nomogram, patients with either tubular or colloid carcinoma were matched on a 1:1 basis with patients resected for conventional ductal pancreatic adenocarcinoma. Clinicopathological factors and overall outcome was analyzed between the matched groups. Fifty-nine patients underwent resection for IPMN with an associated invasive carcinoma (IPMN-INV). The estimated 3- and 5-year survival rates were 76 percent and 68 percent, respectively. Tubular carcinoma was present in 35 patients (59 %) and 24 patients (41 %) had colloid carcinoma. Tubular carcinoma subtype (hazard ratio, HR, 3.7, 95 % confidence interval 1.2 to 11.6) and the presence of positive regional lymph nodes (HR 3.2 95 % confidence interval 1.2 to 8.2) were clinicopathological factors predictive of decreased survival by multivariate analysis. The 5-year estimated survival rates for tubular carcinoma and colloid carcinoma were 55 percent and 87 percent, respectively, which was a significant difference. When compared with patients with conventional ductal pancreatic ductal adenocarcinoma resected during the same time period matched by a prognostic nomogram, patients with colloid carcinoma had a significantly longer survival outcome compared with patients with conventional adenocarcinoma. By contrast, survival after resection between

patients with the tubular subtype (3-year estimated survival, 61 %) and the matched group with conventional adenocarcinoma (3-year estimated survival, 21 %) was not statistically different. In this study, the colloid carcinoma histological subtype of invasive IPMN had a more statistically favorable survival outcome than the tubular subtype. Patients with invasive tubular IPMN had no statistically significant difference in survival as matched patients with conventional ductal pancreatic carcinoma [450].

Mucinous cystic neoplasm and intraductal papillary mucinous neoplasm are two types of cystic pancreatic mucinous tumors, each with its own distinct clinicopathologic features and pathogenetic mechanisms. It was reported an unusual pancreatic mucinous neoplasm with features of both a mucinous cystic neoplasm and an intraductal papillary mucinous neoplasm in a 40-year-old woman who underwent total pancreatectomy. The endoscopic retrograde cholangiopancreatogram and gross examination demonstrated a mucin-producing intraductal neoplasm involving the length of the main pancreatic duct, typical of main duct intraductal papillary mucinous neoplasm, but histology of the main duct showed involvement by a biphasic tumor composed of columnar epithelium overlying ovarian-type stroma, characteristic of a mucinous cystic neoplasm. Immunohistochemistry confirmed that the stromal cells expressed estrogen and progesterone receptors, inhibin, and calretinin [451].

Subtypes

Invasive cancers arising from intraductal papillary mucinous neoplasm (IPMN) are recognised as a morphologically and biologically heterogeneous group of neoplasms. Less is known about the epithelial subtypes of the precursor IPMN from which these lesions arise. The authors investigated the clinicopathological characteristics and the impact on survival of both the invasive component and its background IPMN. The study cohort comprised 61 patients with invasive IPMN (study group) and 570 patients with pancreatic ductal adenocarcinoma (PDAC, control group) resected at a single institution. Multivariate analyses were performed using a stage-matched Cox proportional hazard model. The histology of invasive components of the IPMN cohort was tubular in 38 (62 %), colloid in 16 (26 %), and oncocytic in seven (12 %). Compared with PDAC, invasive IPMNs were associated with a lower incidence of adverse pathological features and improved mortality by multivariate analysis (hazard ratio 0.58; 95 % confidence interval 0.39 to 0.86). In subtype analysis, this favourable outcome remained only for colloid and oncocytic carcinomas, while tubular adenocarcinoma was associated with worse overall survival, not significantly different from that of PDAC (hazard ratio 0.85; 95 % confidence interval 0.53 to 1.36). Colloid and oncocytic carcinomas arose only from intestinal- and oncocytic-type IPMNs, respectively, and were mostly of the main-duct type, whereas tubular adenocarcinomas primarily originated in the gastric background, which was often associated with branch-duct IPMN. Overall survival of patients with invasive adenocarcinomas arising from gastric-type IPMN was significantly worse than that of patients with non-gastric-type IPMN. Tubular, colloid and oncocytic invasive IPMNs have varying prognosis, and arise from different epithelial subtypes. Colloid and oncocytic types have markedly improved biology, whereas the tubular type has a course that resembles PDAC. Analysis of these subtypes indicates that the background epithelium plays an equally, if not more, important role in defining the biology and prognosis of invasive IPMNs [452].

Although intestinal-type intraductal papillary mucinous carcinoma (IPMC) is reported to have a better prognosis, few studies have addressed its invasive pattern. The meaning of "minimal invasion" (MI) in IPMC also remains unclear. It was investigated the prognosis of intraductal papillary mucinous neoplasm (IPMN) focusing on MI and subtypes. It was evaluated 71 patients with IPMC among a total of 179 patients with resected IPMN. Although 2 of 10 MI-IPMC patients had lymph node metastasis, there were no disease-specific deaths among the

MI-IPMC patients. Minimally invasive IPMCs were significantly more frequently observed in intestinal-type IPMC (23/33 cases) than in non-intestinal-type IPMCs (16/38 cases). Among 32 patients with massively invasive IPMC, the prognosis was significantly better for patients with intestinal-type IPMC than for patients with non-intestinal-type IPMC. When confined to massively invasive IPMC, tubular invasion and lymphatic or serosal invasion were less frequently observed in intestinal-type IPMC than in non-intestinal-type IPMC. It was concluded that Invasive carcinoma derived from intestinal-type IPMN is associated with "minimal invasion", colloid carcinoma, and less invasive behavior [453].

Intraductal papillary mucinous neoplasm (IPMN) consists of four epithelial subtypes. Of those, pancreatobiliary and oncocytic types are recently recognized and relatively uncommon, and usually exhibit high-grade dysplasia. The biological properties and molecular characteristics of these two types have not been well documented. The few molecular studies of the oncocytic type showed absence of KRAS mutations commonly seen in the other subtypes, raising the possibility that the oncocytic type is distinct from the other subtypes. Thus, it was examined clinicopathological features and molecular alterations of the two subtypes. The study cohort consisted of 12 pancreatobiliary and 18 oncocytic IPMN cases. KRAS, BRAF, and PIK3CA mutations and TP53, SMAD4, and beta-catenin expression were analysed, and the results of molecular and clinicopathological profiles were compared between the two subtypes. KRAS mutations were identified in the oncocytic type, but less frequently than the pancreatobiliary type (17 % vs 58 %). BRAF mutation was found in a single oncocytic tumour, and no PIK3CA mutations were seen in any of the study cohort. TP53 overexpression was less frequent in the oncocytic type than in the pancreatobiliary type (11 % vs 58 %). Invasive components were present in 50 percent of the oncocytic and 92 percent of the pancreatobiliary types, with lymph node metastasis more frequently seen in the latter, corresponding to better outcomes in the former (5-year survival rates: 93 % vs 32 %). Our demonstration of KRAS and BRAF mutations in the oncocytic-type IPMN supports a role for the activation of the RAS-MAPK pathway in this tumour type. However, the less frequent TP53 overexpression associated with the significantly lower rates of invasion and nodal disease in the oncocytic type correlates with better outcomes compared to the pancreatobiliary type [454].

Natural history

Natural history of main duct IPMNs

Because the prevalence of carcinoma is high in main-duct intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, surgical resection is recommended for all main-duct type IPMNs. One study aimed to investigate the clinical predictors of malignancy and natural history of main-duct IPMNs. Methods: Preoperative clinical characteristics reliably correlated with malignancy in 26 surgically resected patients with main-duct IPMN, and long-term outcome in 20 conservatively followed patients with main-duct IPMN was examined. Age at diagnosis was significantly older in conservatively followed IPMN patients than in surgically resected IPMN patients. Main pancreatic duct (MPD) dilatation 10 mm or greater and mural nodules were significantly more frequent in malignant IPMNs. Obvious progression of dilatation of the MPD was detected in all 4 conservatively followed patients who developed invasive pancreatic carcinoma. The histology of IPMN at autopsy of 4 conservatively followed patients who died of other causes 21 to 120 months later was adenoma. Seven conservatively followed without malignant findings did not show obvious progression of MPD dilatation. It was concluded that although surgical resection is indicated for many main-duct IPMNs, conservative follow-up may be an option for elderly asymptomatic patients with main-duct IPMNs with the MPD less than 10 mm, no obvious mural nodule, and negative cytology [455].

Natural history of branch duct IPMNs

The aim of one study was to evaluate the long-term follow-up results of patients with branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) without mural nodules at 10 representative institutions in Japan. It was analyzed 349 follow-up BD-IPMN patients who had no mural nodules on endoscopic ultrasonography at initial diagnosis. Observation periods ranged from 1 to 16 years (median 4 years). Sixty-two (18 %) patients exhibited disease progression during follow-up. Twenty-two underwent surgery, leading to a pathological diagnosis of carcinoma in 9 and adenoma in 13. Although the remaining 287 (82 %) showed no changes, 7 underwent surgery because of symptoms (n=2), choice (n=2), or development of pancreatic ductal adenocarcinoma (n=3); all of them were diagnosed pathologically as adenomas. Of the 29 patients undergoing surgery, all 9 with carcinoma exhibited signs of progression, such as increased main pancreatic duct diameter and/or appearance of MNs. Pancreatic ductal adenocarcinomas and additional BD-IPMNs developed in 7 (2 %) and 13 (4 %), respectively. Overall, 320 (92 %) patients were followed without surgery. Most BD-IPMN patients who had no mural nodules on endoscopic ultrasonography could be managed without surgery. However, careful attention should be paid to disease progression and the development of pancreatic ductal adenocarcinomas during follow-up [456].

Growth rate

Little information is available about the clinico-pathologic characteristics of pancreatic branch duct intraductal papillary mucinous neoplasm (Br-intraductal papillary mucinous neoplasm [IPMN]) because of difficulties in diagnosis based on radiologic and tissue information. It was investigated the natural history of Br-IPMN using imaging and surgical pathology data from patients. Data were collected from patients admitted to a single tertiary referral institution from 2000 to 2009 (median follow up of 28 months); 201 patients were diagnosed with Br-IPMN with an initial cyst less than 30 mm without main pancreatic duct dilatation or mural nodules. The patients were followed for more than 3 months and examined by computed tomography (CT) at least twice. The mean size of the patients' initial cysts was 15 mm; the mean cyst growth rate was 1.1 mm/year. Thirty-five patients received surgery during follow up and 8 were confirmed to have malignant cysts. The malignant cysts were greater in final size than nonmalignant cysts (24 mm vs 17 mm); they also grew by a greater percentage (69 % vs 19 % and at a greater rate (4 mm vs 1 mm/year). The actuarial 5-year risk of malignancy was 42 percent in the group that received surgery and 11 percent for all patients. Cysts that grew more than 2 mm/year had a higher risk of malignancy (5-year risk = 46 % vs 2 %). It was concluded that in combination with cyst size and the presence of mural nodules, cyst growth rate could be used to predict malignancy in patients with Br-IPMN [457].

Diagnostics

PET

Since 2006 the International Consensus Guidelines (ICG) have been used to choose immediate surgery or surveillance for IPMN patients, but their low specificity increases the number of benign IPMNs that undergo resective surgery. PET has proved highly sensitive and specific in detecting malignancy in cystic neoplasms of the pancreas, including IPMNs. To assess the reliability of the International Consensus Guidelines and 18-fluorodeoxyglucose positron emission tomography (PET) in distinguishing benign from malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, patients suspected with IPMNs of the pancreas seen from 1989 to 2010 were identified and classified as cases of main duct, mixed type and branch type IPMN. The indication for resection or

surveillance was verified a posteriori for all patients according to the ICG. PET was considered positive for a Standardized Uptake Value ≥ 2.5 . Surveillance included clinical examination, laboratory tests, CA 19-9 serum levels, and computed tomography and/or magnetic resonance and magnetic resonance cholangiopancreatography every 6 months for 2 years and yearly thereafter. Endoscopic ultrasound was rarely performed. PET was repeated in clinically or radiologically suspect cases, or if tumor markers increased. Sixty-one main duct or mixed type and 101-branch type IPMNs were included in the study. A histological diagnosis was available for 81 of 162 patients, missing for 1 locally advanced IPMN, whereas 62 patients are under surveillance and it proved impossible to contact 18. Conservative surgery was performed in 16 of 68 patients with benign IPMNs. The sensitivity, specificity, positive and negative predictive value, and accuracy of the ICG in detecting malignancy were 93, 22, 59, 72.7, and 61 percent, whereas for PET they were 83, 100, 100, 85, and 91 percent. It was concluded that PET is more accurate than the ICG in distinguishing benign from malignant (invasive and noninvasive) IPMNs. Prophylactic IPMN resection in young patients fit for surgery should be guided by the ICG, whereas PET should be performed in older patients, cases at increased surgical risk, or when the feasibility of parenchyma-sparing surgery demands a reliable preoperative exclusion of malignancy [458].

True-cut biopsy

Recent data demonstrate the presence of two autoimmune pancreatitis (AIP) subtypes. All existing endoscopic ultrasonography-guided trucut biopsy (EUS-TCB) data pertain to type 1 disease. The aim was now to determine if EUS-TCB samples are sufficient for diagnosing type 2 AIP. This was a retrospective case series conducted in an academic tertiary care center. Patients included those with type 2 AIP (n=5), retrospectively identified from a database of all patients with AIP, diagnosed by HISORT criteria (n=125). The primary outcome measure was the diagnostic capability of EUS-TCB for type 2 AIP. Five patients (4 male, 1 female; mean age 40 years) who underwent EUS-TCB were diagnosed with type 2 AIP. The serum IgG₄ level was elevated in 1 of the 4 patients tested. CT/MRI revealed diffuse pancreas enlargement (n=3), a pancreas head mass (n=1), and a normal pancreas (n=1). Prior to EUS, AIP was not specifically suspected, but part of a broad differential (n=3) or not suspected at all (n=2). Fine-needle aspiration was negative for neoplasia and AIP. The TCB histology was definitive (n=4) or suggestive (n=1) for type 2 AIP. No complications developed [459].

Markers of senescence

Intraductal papillary mucinous neoplasm of the pancreas is attracting attention as a precursor lesion of the invasive ductal adenocarcinoma, whereas it has been reported that some intraductal papillary mucinous neoplasms do not display progression to malignancy and remain almost unchanged in size and morphology. Recent studies have reported that oncogene-induced senescence has been observed in neoplasms, especially in premalignant lesions, and that it can play an important role in preventing malignant progression. To clarify the presence of senescence in intraductal papillary mucinous neoplasms, it was analyzed the expression of several markers of senescence. The intraductal papillary mucinous neoplasms evaluated in this study were classified into 4 groups according to the degree of dysplasia. Senescence-associated beta-galactosidase activity and senescence-associated heterochromatin foci formation were investigated in 33 cases of intraductal papillary mucinous neoplasms and 6 normal controls. Immunohistochemical analysis of p16(INK4a) and p15(INK4b) was performed in 158 cases of intraductal papillary mucinous neoplasms and 10 normal controls. In the normal controls, neither senescence-associated β -galactosidase activity nor senescence-associated heterochromatin foci formation was observed. Most of the normal epithelia were negative for either p16(INK4a) or p15(INK4b).

For all 4 markers, the percentages of positive cases reached a peak in intraductal papillary mucinous neoplasm with low-grade dysplasia and showed significant decreasing trends in the transition from intraductal papillary mucinous neoplasm with low-grade dysplasia to intraductal papillary mucinous neoplasm with an associated invasive carcinoma. Our results indicate that senescence is induced in the early stage of intraductal papillary mucinous neoplasm and gradually attenuated according to the progression. It is suggested that senescence plays a role in preventing malignant progression of intraductal papillary mucinous neoplasm [460].

Prognostic factors

The aim of one study was to define the relevance of mural nodules (MNs) as a "direct" indicator of malignancy of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Thirty-nine surgically resected IPMNs excluding obviously invasive carcinomas were examined. The distribution of the most severely dysplastic lesions was mapped on specimens. Immunohistochemical analysis for MUC1 and MUC2 was performed on sections containing the histologically predominant lesions and the most severely dysplastic areas. The presence of MNs correlated significantly with the histological grade of IPMN; however, the most severely dysplastic lesions were associated with a flat/nonelevated area rather than MNs (79 %). In the MUC1-positive subgroup, minimally invasive carcinoma was colocalized to MNs, whereas most severely dysplastic foci including minimally invasive carcinoma with components of mucinous and tubular adenocarcinoma were observed in the areas apart from MNs in the MUC2-positive and MUC1/2-negative subgroups, respectively. It was concluded that although the data support the concept that MNs represent areas of higher-grade dysplasia within IPMN, development of invasive lesions from MNs may be limited to cases that are MUC1-positive. Careful attention should be paid to the emergence of invasive IPMN from flat foci in MUC2-positive and MUC1/2-negative cases [461].

Tumor markers

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas has malignant potential. Although serum levels of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) are known to be raised in pancreatic ductal adenocarcinoma, little has been reported about their significance in IPMN. Preoperative CA19-9 and CEA levels were measured in consecutive patients undergoing surgical resection for IPMN. Results were correlated with histopathological and clinical features. In 142 patients, raised CEA and CA19-9 serum levels were significantly associated with invasiveness in both branch-duct and main-duct/mixed-type IPMN. Some 74 percent of patients with an invasive IPMN had raised levels of CA19-9, compared with only 14 percent who had non-invasive tumours. With a cut-off level of 37 units/ml, CA19-9 had a specificity of 86 percent, a negative predictive value of 86 percent, a positive predictive value of 74 percent and accuracy of 82 percent. Overall, 80 percent of patients with an invasive IPMN had raised serum levels of CA19-9 and/or CEA compared with only 18 percent of those with a non-invasive tumour. Serum CA19-9 is a useful non-invasive preoperative tool for differentiating between invasive and benign IPMN, and should be taken into account in the decision to offer surgery. Patients with an IPMN and positive tumour markers have a high risk of malignant diseases [462].

Mural nodules

One study aimed to elucidate the preoperative clinical factors that identify high-risk malignant transformation in branch duct-type IPMN. It was retrospectively evaluated 38 patients diagnosed with branch duct-type IPMN who underwent pancreatectomy, identifying different

preoperative factors between adenoma (intraductal papillary mucinous adenoma, IPMA) and carcinoma (intraductal papillary mucinous carcinoma, IPMC). Twelve patients were diagnosed with IPMC. The mean tumor size was 32 ± 12 mm for IPMA and 36 ± 17 mm for IPMC. No significant differences were found between IPMA and IPMC patients with regard to age, gender, symptoms, and tumor number. The mean diameter of the main pancreatic duct was significantly larger in IPMCs (8 ± 6 mm) compared with IPMAs (5 ± 2 mm). The mural nodule was a good predictor of malignancy and was identified as the only independent and significant marker of IPMC in multivariate analysis. The presence of mural nodules is a potentially suitable marker for differentiating IPMC from IPMA, and is important for making decisions about surgical interventions [463].

After resection

Survival after resection for invasive intraductal papillary mucinous neoplasm (inv-IPMN) is superior to pancreatic ductal adenocarcinoma (PDAC). This difference may be explained by earlier presentation of inv-IPMN. It was hypothesized that inv-IPMN has survival comparable with PDAC after resection when matched by stage. From 1999 to 2009, 113 patients underwent resection for inv-IPMN at 2 large academic institutions. These data were compared with 845 patients during the same period undergoing resection for PDAC. Demographics, pathology, and overall survival (OS) were compared according to current American Joint Committee on Cancer stage. Mean age with inv-IPMN and PDAC was 68 and 65 years, respectively. Follow-up was 33 and 24 months for inv-IPMN and PDAC, respectively. Median OS was 32 months for inv-IPMN and 17 months in PDAC. Median OS in lymph node-negative inv-IPMN was 41 months and 24 months in PDAC, with the greatest absolute difference in stage Ia patients with OS of 80 and 50 months in inv-IPMN and PDAC, respectively. In node-positive patients, OS was 20 months in inv-IPMN and 15 months in PDAC. Of inv-IPMN, 24 percent was colloid versus 75 percent of tubular subtype; 37 (85 %) of node-positive inv-IPMN were tubular subtype. Median OS was 23 and 127 months for tubular and colloid subtypes, respectively. When matched by stage, inv-IPMN has superior survival after resection compared with PDAC. This disparity is greatest in node-negative and least in node-positive disease. These findings suggest the behaviors of inv-IPMN and PDAC, although different, converge with advancing American Joint Committee on Cancer stage because of a greater proportion of tubular subtype [464].

IPMN causing acute pancreatitis

Intraductal papillary mucinous neoplasms (IPMNs) are cystic pancreatic tumors that arise from the pancreatic ducts and are increasingly reported worldwide. Both benign and malignant tumors of the pancreas are thought to contribute to recurrent pancreatitis possibly by pancreatic duct obstruction, and IPMNs contribute to a major share of this burden. The rate of acute pancreatitis (AP) in IPMN patients in the largest published surgical series has varied from 12 to 67 percent. IPMN may be categorized into 3 forms on the basis of the areas of involvement: main pancreatic duct (MD-IPMN), side branch (SB-IPMN), or combined. Both MD-IPMN and SB-IPMN may be the cause of pancreatitis. The risk of AP seems to be similar with both main duct IPMN and SB-IPMN, although data are controversial. AP in IPMN patients is not severe and often recurs without treatment. The rate of AP does not seem to differ among benign and malignant IPMNs, and the correlation between the malignant potential and the occurrence of AP is ill defined. AP seems to occur more often in patients with IPMN than in those with usual pancreatic adenocarcinoma possibly because of obstruction of the main duct by thick, abundant mucus secretion. Although the Sendai guidelines recommend surgical resection in patients with SB-IPMN with AP, data are controversial. Moreover, in patients with an episode of pancreatitis, the finding

of pancreatic cysts is often attributed to pseudocysts or fluid collections that make the diagnosis of IPMN less suspicious. Future longitudinal and prospective studies to understand the natural history of AP in patients with IPMN are required to better manage patients with recurrent AP in the setting of IPMN [465].

Surgery

Because of the malignant potential, resection has been recommended for some intraductal papillary mucinous neoplasms (IPMN). We hypothesize that a large cancer database could be used to evaluate national resection rates and survival for malignant IPMN. Using the Surveillance Epidemiology and End Results (SEER) database, 1988-2003, cases of malignant IPMN were identified using histology codes. Of 1834 patients, 209 (11 %) underwent resection. Annual age-adjusted incidence decreased over the study time-course, while annual proportion of patients presenting with localized lesions and the proportion being resected increased. Predictors of resection on multivariate analysis included localized stage, and more recent diagnosis. Median survival for resected patients was 16 months versus 3 months without resection. After adjusting for age, gender, stage, year, and tumor location, surgical resection remained a significant predictor of survival (hazard ratio 0.44). It was concluded that in this population-based cohort, detection of malignant IPMNs is decreasing, with an increasing proportion of patients diagnosed at local stages and undergoing resection. Increased awareness of IPMN may be contributing to earlier detection, which might include benign/premalignant lesions, and greater utilization of resection for appropriate candidates; thus, we may be improving survival for this most treatable form of pancreatic cancer [466].

Ethanol lavage

Determine the effectiveness of multiple endoscopic ultrasound-guided ethanol lavage (EUS-EL) sessions for attempted ablation of pancreatic cystic lesion (PCL) was done by a retrospective review of patients who have undergone 2 or more EUS-EL treatments of a PCL. Eligible patients had asymptomatic, benign-appearing PCL, no previous pancreatitis, and were considered poor surgical candidates. Final analysis was performed on 13 patients with suspected branch duct intraductal papillary mucinous neoplasms. The mean maximum cyst diameter at baseline and after 1 and 2 EUS-EL treatments was 20 ± 7 , 17 ± 10 , and 13 ± 10 mm, respectively. Complete resolution of the cystic lesion was not seen by computed tomography or magnetic resonance imaging in any patient after 1 EUS-EL but occurred in 5 (38 %) of 13 patients after 2 EUS-EL treatments. One patient had minor abdominal pain 1 day after the first EUS-EL session and 2 days after the second session. It was concluded that compared with only 1 EUS-EL, 2 EUS-EL treatment results in a significantly greater decrease in the size and surface area of PCL and is associated with a significantly higher rate of image-defined cyst resolution [467].

Intraductal tubulopapillary neoplasm

Intraductal tubulopapillary neoplasm (ITPN) is a recently recognized rare variant of intraductal neoplasms of the pancreas. Molecular aberrations underlying the neoplasm remain unknown. It was investigated somatic mutations in PIK3CA, PTEN, AKT1, KRAS, and BRAF. It was also investigated aberrant expressions of phosphorylated AKT, phosphatase and tensin homolog (PTEN), tumor protein 53 (TP53), SMAD4, and CTNNB1 in 11 cases of ITPNs and compared these data with those of 50 cases of intraductal papillary mucinous neoplasm (IPMN), another distinct variant of pancreatic intraductal neoplasms. Mutations in PIK3CA were found in 3 of 11 ITPNs but not in IPMNs. In contrast, mutations in KRAS were

found in none of the ITPNs but were found in 26 of the 50 IPMNs. PIK3CA mutations were associated with strong expression of phosphorylated AKT. Moreover, the expression of phosphorylated AKT was apparent in most ITPNs but only in a few IPMNs. Aberrant expressions of TP53, SMAD4, and CTNNB1 were not statistically different between these neoplasms. Mutations in PIK3CA and the expression of phosphorylated AKT were not associated with age, sex, tissue invasion, and patients' prognosis in ITPNs. These results indicate that activation of the phosphatidylinositol 3-kinase pathway may play a crucial role in ITPNs but not in IPMNs. In contrast, the mutation in KRAS seems to play a major role in IPMNs but not in ITPNs. The activated phosphatidylinositol 3-kinase pathway may be a potential target for molecular diagnosis and therapy of ITPNs [468].

Intraductal papillary neoplasms of the bile duct (IPNB)

Intraductal papillary neoplasms of the bile duct (IPNB) have been recently proposed as the biliary counterpart of intraductal papillary mucinous neoplasms of the pancreas (IPMN-P). However, in contrast to IPMN-P, IPNB include a considerable number of the tumors without macroscopically visible mucin secretion. It was reported the similarities and differences between IPNB with and without macroscopically visible mucin secretion (IPNB-M and IPNB-NM). Surgically resected 27 consecutive cases with IPNB were divided into IPNB-M (n=10) and IPNB-NM (n=17), and their clinicopathologic features were examined. Clinically, both tumors were similar. Pathologically, the most frequent histopathologic types were pancreatobiliary in IPNB-NM and intestinal in IPNB-M. Various degrees of cytoarchitectural atypia within the same tumor were exhibited in 8 IPNB-M, but only 3 in IPNB-NM. Although the tumor size was similar, 9 IPNB-NM were invasive carcinoma, whereas all but 1 IPNB-M with carcinoma were in situ or minimally invasive. Immunohistochemically, positive MUC2 expression was significantly more frequent in IPNB-M than in IPNB-NM, whereas MUC1 tended to be more frequently expressed in IPNB-NM compared with IPNB-M. Among IPNB-NM with positive MUC1 expression, 3 had negative MUC2 and MUC5AC expressions. These tumors showed a tubulopapillary growth with uniform degree of cytoarchitectural atypia. All IPNB-M were negative for p53, and the frequency of positive p53 protein in IPNB-NM was at the middle level of that in IPNB-M and nonpapillary cholangiocarcinoma. In conclusion, IPNB-M showed striking similarities to IPMN-P, but IPNB-NM contained heterogeneous disease groups [469].

Intraductal papillary neoplasm (IPN) of the bile duct is a newly described pathologic entity characterized by the presence of intraluminal tumors, which sometimes produce a large amount of mucin and form a cystic tumor. Cystic IPN of the bile duct is different from biliary cystadenoma or cystadenocarcinoma in that the former produces intraductal microscopic and macroscopic papillary tumors without ovarian-like stroma, whereas the latter produce a mucin-containing septate cystic tumor without communication with bile duct and with ovarian-like stroma in the cyst wall. The purpose of one study was to evaluate the potential relationships between cyst-forming IPNs of the bile duct and peribiliary glands and also intraductal papillary mucinous neoplasms of the pancreas. From a cohort of 87 patients with surgically resected and pathologically proved IPN of the bile duct, 12 patients with cystic IPN of the bile duct who underwent CT (n=12), MRCP (n=3), ultrasound (n=3), and ERCP (n=4) were included. Imaging findings were evaluated for the relationship of cystic tumors to the bile ducts; in particular, a diverticulum-like appearance was considered as suggestive of the peribiliary gland origin. Pathologic examination was conducted, and both gross and microscopic findings were recorded. Radiologic examination revealed aneurysm-like dilatation of the involved bile ducts in five patients and intrahepatic biliary cystic tumor in two patients. Interestingly, the remaining five patients had diverticulum-like cystic tumor with or without communication; one patient had a cystic tumor laterally attached to the extrahepatic bile duct. Histopathologically, cystic tumors are lined by atypical biliary epithelium showing intracystic papillary proliferation, with an appearance similar to that of pancreatic intraductal papillary mucinous neoplasm. The study suggests that cyst-forming IPN of the bile duct may

be a biliary counterpart to pancreatic intraductal papillary mucinous neoplasm. In particular, at least some of the tumors seem to arise from peribiliary glands, and these cases might be a counterpart to branch-duct intraductal papillary mucinous neoplasm of the pancreas, given the histologic similarity between peribiliary glands and pancreatic branch ducts [470].

OTHER NEOPLASTIC CYSTIC PANCREATIC TUMORS

Cystic lesions of the pancreas are being identified more frequently, and a selective approach to resection is now recommended. The aim of one study was to assess the change in presentation and management of pancreatic cystic lesions evaluated at a single institution over 15 years. A prospectively maintained registry of patients evaluated between 1995 and 2010 for the ICD-9 diagnosis of pancreatic cyst was reviewed. The 539 patients managed from 1995 to 2005 were compared with the 885 patients managed from 2005 to 2010. A total of 1,424 patients were evaluated, including 1,141 with follow-up >6 months. Initial management (within 6 months of first assessment) was operative in 422 patients (37 %) and nonoperative in 719 patients (63 %). Operative mortality in patients initially submitted to resection was 0.7 percent (n=3). Median radiographic follow-up in patients initially managed nonoperatively was 28 months (range 6 to 175 months). Patients followed radiographically were more likely to have cysts that were asymptomatic (72 % vs 49 %), smaller (1.5 vs 3 cm), without solid component (94 % vs 68 %), and without main pancreatic duct dilation (88 % vs 61 %). Changes prompting subsequent operative treatment occurred in 47 patients (7 %), with adenocarcinoma identified in 8 (17 %) and pancreatic endocrine neoplasm in 4 (9 %). Thus, of the 719 patients initially managed nonoperatively, invasive malignancy was identified in 12 (2 %), with adenocarcinoma seen in 1 percent. It was concluded that cystic lesions of the pancreas are being identified more frequently, yet are less likely to present with concerning features of malignancy. Carefully selected patients managed nonoperatively had a risk of malignancy that was equivalent to the risk of operative mortality in those patients who initially underwent resection [471].

Guidelines

Evaluation of the value of cytology relative to imaging features in risk assessment for malignancy as defined in the Sendai Guidelines was performed. The Sendai Guidelines list symptoms, cyst size >30 mm, dilated main pancreatic duct (MPD) >6 mm, mural nodule (MN) and "positive" cytology as high risk stigmata for malignancy warranting surgical triage. It was reviewed clinical, radiological and cytological data of 112 patients with histologically confirmed mucinous cysts of the pancreas evaluated in a single tertiary medical center. Cytology slides were blindly re-reviewed and epithelial cells grouped as either benign or high-grade atypia (HGA), i.e. \geq high-grade dysplasia. Histologically, neoplasms were grouped as benign (low-grade and moderate dysplasia) and malignant (in situ and invasive carcinoma). Performance characteristics of cytology relative to other risk factors were evaluated. Dilated MPD, MN, and HGA were independent predictors of malignancy, but not symptoms or cyst size >30 mm. HGA was the most sensitive predictor of malignancy in all cysts (72 %) and in small (\leq 30 mm) branch-duct intraductal papillary mucinous neoplasm (BD IPMN; 67 %), whereas also being specific (85 and 88 %, respectively). MN and dilated MPD were highly specific (>90 %), but insensitive (39 %-44 %). Cytology detected 30 percent more cancers in small cysts than dilated MPD or MN and half of the cancers without either of these high-risk imaging features. Cytology adds value to the radiological assessment of predicting malignancy in mucinous cysts, particularly in small BD IPMN [472].

Diagnostics

Endoscopic ultrasonography

A retrospective review was conducted to determine the utility of endoscopic ultrasound (EUS) examination of the pancreas after initial pancreatic cyst detection with cross-sectional imaging. Initial cross-sectional imaging reports were reviewed and compared to subsequent EUS findings. Findings evaluated included cyst size, number, multifocality, presence in different surgical fields, cyst wall nodularity, main pancreatic duct (PD) dilation, communication with PD, and features suggestive of serous cystadenoma. Compared to computed tomographic scan, EUS more frequently identified pancreatic cystic lesion multifocality (47 % vs 13 %) and their presence in different surgical fields (33 % vs 4 %). Compared to magnetic resonance imaging, EUS was superior in identifying multifocality (58 % vs 34 %) and the presence of cysts in different surgical fields (42 % vs 26 %). Malignancy was suspected or confirmed in 3 patients by EUS fine-needle aspiration cytology, not suspected by cross-sectional imaging. Endoscopic ultrasound identified unappreciated features of serous cystadenomas in 10 patients. It was concluded that endoscopic ultrasound identified synchronous pancreatic cystic lesions unappreciated by initial cross-sectional imaging, with undetected cysts frequently outside of typical resection margins. In addition, EUS identified the presence of unappreciated high- or low-risk characteristics in a small percentage of patients [473].

CT

The objective of one article was to evaluate the accuracy of MDCT features of pancreatic cystic lesions in cyst characterization and in predicting cyst biologic aggressiveness. In this prospective study, 114 patients (40 men and 74 women; age range, 23-89 years) with 130 cystic lesions (size range, 31-160 mm) in the pancreas underwent contrast-enhanced dual-phase (n=92) and portal phase (n=22) examinations with 16- or 64-MDCT scanners. Using defined morphologic features of cystic lesions on MDCT, two readers performed blinded evaluations for cystic characterization and predicting biologic aggressiveness (invasive lesions, carcinoma in situ, and moderate grade dysplasias) before pancreatic surgery. Receiver operating characteristic analysis was performed to assess the accuracy of MDCT using pathologic evaluation of the surgical specimen as a reference standard. On the basis of MDCT features, the radiologic accuracy (reader 1 and reader 2) for stratifying lesions into mucinous and nonmucinous subtypes was 85 percent and 82 percent and for recognizing cysts with aggressive biology was 86 percent and 85 percent, respectively. Predictive values of MDCT were superior for lesions > 30 mm and nonmucinous lesions. Features favoring aggressive biology were main pancreatic duct dilation > 10 mm, biliary obstruction, mural nodule, main-duct intraductal papillary mucinous neoplasm, and advanced age. Sensitivity of detecting morphologic features was higher with the dual-phase pancreatic protocol CT. Morphologic features of pancreatic cystic lesions on MDCT allow reliable characterization into mucinous and nonmucinous subtypes and enable prediction of biologic aggressiveness [474]

MRI

Pancreatic cystic lesions are increasingly being recognized. Magnetic resonance imaging (MRI) is the method that brings the greatest amount of information about the morphologic features of pancreatic cystic lesions. To establish if diffusion-weighted MRI (DW-MRI) can be used as a tool to differentiate mucinous from nonmucinous lesions 56 patients with pancreatic cystic lesions (benign, n =46; malignant, n = 10) were prospectively evaluated with DW-MRI in order to differentiate mucinous from nonmucinous lesions. Final diagnosis was obtained by follow-up (n = 31), surgery (n = 16) or endoscopic ultrasound-guided fine

needle aspiration (n = 9). Serous cystadenoma was identified in 32 (57%) patients. Results: The threshold value established for the differentiation of mucinous from nonmucinous lesions was 2,230.06 s/mm² for ADC of 700. DWI-MRI behavior between mucinous and nonmucinous groups revealed sensitivity, specificity, positive predictive value, negative predictive value and accuracy to be 80, 98, 92, 93 and 93 percent, respectively. In the comparison of the diffusion behavior between mucinous (n=13) and serous (n=32) lesions, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 100, 97, 92, 100 and 98 percent, respectively. The results of endoscopic ultrasound-guided fine needle aspiration were similar to those of DW-MRI. It was concluded that DW-MRI can be included as part of the array of tools to differentiate mucinous from nonmucinous lesions and can help in the management of pancreatic cystic lesions [475].

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Cyst fluid K-ras

Benign pancreatic cystic neoplasms are important precursors to pancreatic adenocarcinoma, and offer the opportunity to prevent cancer. Conversely, prevention only occurs with surgical resection associated with significant morbidity and mortality, while the natural history of small cystic neoplasms is a slow and uncertain progression to malignancy. Markers that predict progression to malignancy are needed. Cyst fluid DNA analysis including K-ras mutations may predict more aggressive natural history of pancreatic cystic neoplasms. Sixty patients with pancreatic cysts measuring less than 3 cm without solid component or pancreatic ductal dilation underwent EUS with fine needle aspiration. Nine had surgical resection. Cyst fluid was tested for cytology, CEA levels, and DNA analysis including K-ras mutations, and eight loss of heterozygosity mutations. Mutations were correlated with findings of atypia and CEA levels. Cyst fluid K-ras mutation was found in 30 percent of patients. Patients with mutated K-ras were more likely to have atypia on cytology or pathology (39 vs 14 %) and higher CEA (median 591 vs 42) compared to wild-type K-ras. K-ras mutants were more likely to have two or more loss of heterozygosity mutations. Loss of heterozygosity mutations did not correlate with atypia or CEA levels. It was concluded that cyst fluid K-ras mutation correlates with other markers of aggressive cyst behavior. EUS with cyst DNA analysis may alter management of smaller pancreatic cysts when surgery might otherwise be deferred [477].

CEA and cytology

Endoscopic ultrasound (EUS) may offer a diagnostic tool through the combination of imaging and guided fine-needle aspiration of pancreatic cysts. The purpose of one investigation was to determine the most accurate test for differentiating mucinous from nonmucinous cysts. The results of EUS imaging, cytology, and cyst fluid biochemical markers were prospectively collected and compared in a large single-center study (776 patients) using histology or malignant cytology as the final diagnostic standard in 198 patients. The mean cyst fluid carcinoembryonic antigen (CEA) was greater in mucinous cysts (4703 ng/mL) compared with nonmucinous cysts (26 ng/mL). When using the optimal cut-off value of 110 ng/mL, the CEA was more accurate (86 %) than EUS imaging (48 %) and cytology (58 %) in predicting a mucinous cyst. Malignant cysts had a mean cyst fluid CEA value (2558 ng/mL) similar to benign cysts (4700 ng/mL). Cytology (75 %) more accurately diagnosed malignant cysts than EUS (66 %) and CEA (62 %). It was concluded that cyst fluid CEA concentration provides a highly accurate test for the diagnosis of a mucinous cyst, but does not distinguish benign from malignant cysts. Cytology is the most accurate test for the diagnosis of a malignant cyst [478].

Serous cystic neoplasms (SCN)

The majority of pancreatic serous cystic neoplasms (SCNs) are benign. However, these neoplasms can cause symptoms and rarely can be aggressive. Identification of factors associated with symptomatic or aggressive SCNs may aid management decisions. The aim of one study was to identify variables that predict aggressive SCNs. A prospective pathology database was queried for SCNs that were surgically resected at Johns Hopkins Hospital. Tumors were considered aggressive if they invaded surrounding structures and/or vessels or if they metastasized to lymph nodes or distant organs. The associations of gender, tumor size, and tumor location, with the presence or absence of symptoms and tumor behavior were examined using Fisher's exact test, logistic regression, and multivariate analyses. A total of 257 patients with SCNs underwent surgical resection. Mean tumor diameter was 4.9 cm. Tumor location in the head of pancreas (HOP) was associated with symptoms (odds ratio (OR) 1.87, 95 % confidence interval 1.1 to 3.3). Computed tomography (CT) predicted the diagnosis of SCN in approximately a quarter of patients. Thirteen tumors (mean 10.5 cm) were considered aggressive. Multivariate analysis showed that tumor diameter (OR 1.53, 95 % confidence interval 1.24 to 1.89) and location of tumor in pancreatic head (OR 10.44, 95 % confidence interval 1.73 to 63.04) were independently associated with aggressive behavior. It was thus described the largest case series of patients with pathologically proven SCNs. CT performed poorly in preoperative diagnosis of SCNs. Large tumor size and head location predicted aggressive behavior. These factors should be considered in the management of patients with pancreatic serous cystic neoplasms [479].

Mucinous cystic neoplasms (MCN)

Pancreatic mucinous cystic neoplasms (MCN) are premalignant lesions whose natural history is poorly known. Whether the dysplasia grade might be determined with precision by preoperative clinical and imaging criteria is not known. It was aimed to determine if CT scan data might be useful to predict the grade of dysplasia in a series of 60 histologically proven MCN. All consecutive patients who were operated on with pathological confirmation of MCN were included. Careful CT scan evaluation was reviewed without knowledge of pathological results. Imaging and pathological results were correlated. Sixty patients (59 females) were included. Low- and intermediate-grade dysplasias were identified in 47 and 3 patients (benign MCN), respectively, and high-grade dysplasia and invasive carcinoma in 7 and 3

patients (malignant MCN), respectively. Patients with benign lesions were significantly younger. None of the studied clinical data were statistically different to distinguish benign and malignant MCN, except age (42 vs 48 years). Only maximal diameter and mural nodules on CT scan were significantly more frequent in the malignant group. No malignant MCN had a maximal diameter <40 mm. At a 40-mm threshold, the sensitivity and specificity of the maximal diameter to diagnose malignant MCN were 100 and 54 percent, respectively. Mural nodules seen on CT scan were confirmed in all cases but one upon pathological examination of the surgical specimen. The sensitivity and specificity of the presence of a mural nodule seen on CT scan for the diagnosis of a malignant lesion were 100 and 98 percent, respectively. Preoperative CT scan detection of a mural nodule within a cystic pancreatic neoplasm suggestive of MCN strongly suggests malignancy. A diameter <40 mm is associated with no risk of malignancy [480].

The aim of the study was to evaluate the utility of diffusion-weighted imaging (DWI), including apparent diffusion coefficient (ADC) measurement, in order to differentiate mucinous cystic neoplasms (MCNs) from intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. Fifty cases of IPMN with a total of 62 lesions, and eight cases of MCN, were retrospectively selected for the study. The cases of IPMN were selected using multimodality clinical or histopathological criteria, while all MCN lesions were histopathologically proven. DWI was carried out using b values of 500 and 1000s/mm². Visual assessment was performed by two radiologists who used two categories (low-iso or high signal intensity). ADC values of the lesions were also calculated. All IPMN lesions demonstrated low-iso signal intensities compared with the pancreatic parenchyma on DWI. Two of the MCN lesions demonstrated low-iso signal intensities, and six lesions demonstrated high signal intensities. The ADC values for IPMNs were significantly higher than those for MCNs. ROC analysis showed an optimal cut-off value for differentiating between the two types of lesions, providing a sensitivity of 98 percentage and a specificity of 88 percentage. The results of the present study suggest that ADC values in mucinous cystic lesions of the pancreas can be advantageous for their characterization into IPMN and MCN [481].

FDG accumulation

It was reported a case of mucinous cystic neoplasm which showed FDG accumulation in its cyst wall. MRI revealed that this tumor had repeated intracystic hemorrhage. Inhomogeneous FDG accumulation was found in the cyst wall. The epithelium was focally denuded and ovarian-like stroma with macrophage migration, which phagocytosed red blood cells, and fibrosis were recognized on histopathological examination. These histopathological findings suggested that FDG accumulates not in the monolayer epithelium but in ovarian-like stroma with macrophage migration and fibrosis. Macrophage migration and fibrosis were considered to have contributed to FDG accumulation in this mucinous cystic neoplasm [482].

CT versus MRI

To estimate the prevalence of focal cystic pancreatic lesions (FCPLs) among patients undergoing computed tomographic (CT) or magnetic resonance (MR) imaging at one institution and to examine any variation in radiologists' recommendation practice pattern with regards to FCPLs. A cohort of patients with FCPLs was identified from radiology reports by using natural language processing. Patient-specific (i.e. age, gender, symptoms, history of pancreatitis), radiologist-specific (i.e. years of experience, area of expertise), and FCPL-specific (i.e. size, location, septation, calcification, mural nodularity, pancreatic duct involvement, and presence of multiple cysts) variables were obtained. The outcome measure was whether a follow-up study was recommended. A logistic regression model was used to identify relative recommendation rates after controlling for key explanatory variables. During 2009, a total of 1067 FCPLs were identified in 765 patients. Prevalence rates ranged from 2

percent at CT to 16 percent at MR imaging. Radiologists recommended a follow-up imaging study in 24 percent of cases of a FCPL. A 2.8-fold difference in the rate of recommendation of further imaging existed across radiologists after controlling for explanatory variables such as lesion-, radiologist-, and patient-specific characteristics. A history of pancreatitis was associated with a nearly two-fold decrease in recommending further imaging. It was concluded that FCPLs are common, and nearly one-quarter of radiology reports recommend at least one follow-up imaging study. Significant variation exists in the rate of recommendation for further imaging studies by radiologists, even after controlling for key explanatory variables [483].

MDCT ± MRI

To assess the diagnostic accuracies of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) for differentiating benign from malignant lesions and suggesting the specific diagnoses for pancreatic cystic lesions, and to assess whether review of both MDCT and MRI is beneficial. Patients with various neoplastic and non-neoplastic pancreatic cystic lesions that were identifiable by biopsy or surgery, who underwent both MRI and MDCT (n=63), were retrospectively reviewed by three reviewers. The likelihood of malignancy was recorded on a five-point scale, and a specific diagnosis was given. ROC analysis was performed and the sensitivity, specificity for the characterization of malignancy, and the accuracy of specific diagnoses were calculated. MDCT and MRI yielded comparable results for the characterization of malignancy. The accuracies of specific diagnosis based on MDCT or MRI were 62 versus 56 percent for reviewer 1; 76 versus 76 percent for reviewer 2; and 65 versus 62 percent for reviewer 3. There was a trend toward better prediction of malignancy and better accuracy in suggesting a specific diagnosis for MDCT+MRI over MDCT or MRI alone, although it was statistically significant for one reviewer in the comparison of MDCT versus MDCT+MRI for the prediction of malignancy, and MRI versus MDCT for suggesting a specific diagnosis. It was concluded that MDCT and MRI have equivalent accuracy for characterizing pancreatic cystic lesions as benign or malignant, and suggesting a specific diagnosis. Combined review of MDCT and MRI was not significantly better but may have the potential to improve diagnostic accuracy in equivocal cases [484].

NON-NEOPLASTIC CYSTIC PANCREATIC TUMORS

Cystic lesions of pancreas are increasingly identified due to widespread use and improved resolution of cross-sectional imaging. Cystic lesions of the pancreas encompass a wide spectrum of pathologic entities with variable morphology, clinical behavior, and pathogenesis. The predominant cystic neoplasms are intraductal papillary mucinous tumors (IPMT), mucinous cystic neoplasms, serous cystic adenomas, and solid pseudopapillary neoplasms. Cystic pancreatic neoplasms are considered malignant or premalignant, except for serous cystic adenomas, which are almost always benign. In contrast, nonneoplastic cysts have no malignant potential and include pseudocysts, retention cysts, benign epithelial cysts, abscesses, duodenal wall cysts (diverticula), lymphoepithelial cysts (LECs), and the recently described mucinous nonneoplastic cyst. The lesions can also be broadly classified into neoplastic and nonneoplastic cysts. Nonneoplastic cysts have no malignant potential and include pseudocysts, retention cysts, benign epithelial cysts, abscesses, duodenal wall cysts (diverticula), lymphoepithelial cysts, and the recently described mucinous nonneoplastic cyst. Although preoperative differentiation of neoplastic and nonneoplastic lesions is not always possible, awareness of key clinical and imaging features is critical in forming a differential diagnosis and guiding treatment [485]

Pseudocysts

Pseudocysts are the most common cystic pancreatic lesion, accounting for approximately 75 percent of pancreatic cysts. They are fully encapsulated pancreatic fluid collections, usually located within or adjacent to the pancreas that require at least 4 weeks to form after acute pancreatitis. Histologically, the pseudocyst wall is nonepithelized, composed of granulation or fibrotic tissue, and contains amylase-rich, possibly hemorrhagic debris. On computed tomography (CT), pseudocysts are round or oval and have a relatively thin (1-2 mm) enhancing fibrous capsule, which may calcify. They contain fluid that is less than 15 Hounsfield units (HU); higher fluid attenuation values of 40-50 HU indicate intracystic hemorrhage. Pseudocysts vary significantly in size and may communicate with the pancreatic duct. On magnetic resonance imaging, they appear as loculated fluid signal intensity collections, possibly communicating with a dilated pancreatic duct. Typical symptoms include epigastric pain and an abdominal mass, along with clinical sequela of gastric outlet and biliary obstruction [485].

Retention cyst

Retention cysts are a segment of pancreatic duct that is cystically dilated because of obstruction. These cystic lesions are caused by obstructing calculi or fibrotic ductal narrowing, as in chronic pancreatitis. Retention cysts are also seen with obstructing viscous mucin, as in cystic fibrosis, or neoplastic infiltration of periductal tissue, as with ductal adenocarcinoma. On imaging, they appear as small loculated fluid collections, which communicate with the pancreatic duct. If a proximal obstructing lesion is identified, confident preoperative diagnosis can be made; otherwise, imaging features overlap with IPMT [485]

Benign epithelial cyst

Benign epithelial cysts, also termed simple or true cysts, consist of a single layer of cuboidal epithelium, which does not communicate with the pancreatic duct. Simple cysts are rare lesions in the adult population and their etiology is unknown; however, the higher prevalence in children supports a congenital origin. Simple pancreatic cysts are present in about 10 percent of patients with autosomal-dominant polycystic kidney disease, thus representing the second most common extrarenal manifestation of autosomal-dominant polycystic kidney disease. Benign epithelial cysts may present with pain and nausea/vomiting, and if large, as an abdominal mass; yet, many patients are asymptomatic. Surgical resection is indicated for symptomatic lesions and often performed for asymptomatic lesions given the inability to exclude a cystic pancreatic neoplasm. Imaging features include a well-defined homogenous fluid collection (usually unilocular) with an imperceptible wall and no mural nodularity, calcification, or enhancement. In addition, the pancreatic duct is normal in caliber without evidence of pancreatitis [485].

Necrosis

Pancreatic necrosis is devitalized pancreatic parenchyma, which appears on intravenous contrast-enhanced imaging as focal or diffuse zones of nonenhancement. CT has an overall accuracy of 87 percent for detection of pancreatic necrosis in the setting of acute pancreatitis. Identification of pancreatic necrosis is important as it directly correlates with length of hospitalization, development of complications, and death; moreover, the extent of necrosis correlates with morbidity and mortality rates. Necrosis occurs in about 20 percent of patients with acute pancreatitis and it usually presents early in their clinical course (within the

first 24-48 hours). The complex pathophysiologic processes that underlie pancreatic necrosis are not completely understood. As sterile necrotic pancreatic tissue undergoes liquefaction, it appears on imaging as an encapsulated nonenhancing fluid collection, which may be mistaken for a cystic pancreatic mass. If bacterial contamination does not occur, these liquefied collections can remain stable, evolve into pseudocysts, or resolve. Secondary infection, usually by Gram-negative intestinal flora, develops in 5-10 percent of patients with pancreatic necrosis. Although infected pancreatic necrosis is suggested by the presence of gas bubbles, diagnosis often requires percutaneous aspiration. Treatment for infected necrosis is surgical debridement [485].

Abscess

Pancreatic abscess is a poorly encapsulated collection of pus usually located in proximity to, but outside, the pancreas. In acute pancreatitis complicated by peripancreatic fluid collections, approximately 3 percent will develop an abscess, usually within 3-4 weeks. Abscess formation begins with extravasation of active pancreatic enzymes resulting in fat necrosis and eventual liquefaction. Once infected, these liquefied collections form abscesses. CT findings include a confined, low-attenuation fluid collection with peripheral enhancement in the setting of sepsis and recent history of pancreatitis. Presence of gas within this loculated fluid collection increases the diagnostic specificity of an abscess, but confirmatory diagnosis requires percutaneous aspiration [485].

Duodenal diverticulum

Duodenal diverticula are smooth round outpouchings of the duodenum, usually located in the medial periampullary region. This proximity to the pancreatic head can cause fluid-filled duodenal diverticula to be mistaken for cystic pancreatic masses on imaging. These lesions are lined by columnar mucin-producing epithelium and may be surrounded by pancreatic acinar tissue. True duodenal diverticula are thought to arise from abnormal recanalization of the duodenal lumen; however, most are pseudodiverticula, resulting from increased intraluminal pressure, causing mucosal herniation through the muscularis at weak points in the wall. Although duodenal diverticula can be symptomatic, resulting in abdominal pain or bleeding, most are asymptomatic. In addition, duodenal diverticula may be associated with chronic pancreatitis confined to the region between the duodenum and pancreatic head, which is known as groove pancreatitis. On CT/magnetic resonance imaging, they often appear as a thin-walled, round fluid collection – containing gas and/or oral contrast/fluid. Lack of either gas or oral contrast within these lesions makes distinction from cystic pancreatic masses challenging, and further evaluation with upper gastrointestinal barium examination may prove diagnostic [485].

Lymphoepithelial cyst

Lymphoepithelial cysts (LECs) are rare lesions, constituting about 0.5 percent of pancreatic cysts, and they predominately occur in middle-aged men (mean age, 55; M/F: 4:1). Clinical symptoms, if present, include abdominal pain, nausea, vomiting, anorexia, and weight loss. LECs are well-delineated multilocular (60 %) or unilocular (40 %) masses of variable size, ranging from about 1 to >15 cm. They are lined by a stratified squamous epithelium and contain subepithelial lymphoid tissue and follicles. The pathogenesis of pancreatic LECs and their relationship to salivary gland LECs is uncertain. Moreover, disease states associated with salivary type, such as Sjogren syndrome, human immunodeficiency virus, and lymphoma, seem to have no association with pancreatic type. On CT, pancreatic lesions are

well-circumscribed low-attenuation masses with a thin enhancing rim, septations, and focal calcification.. Intracystic contents usually measure 20-30 HU due to high levels of keratin. No recurrences or malignant degeneration of LECs are reported in the literature. However, given the difficulty in making a confident preoperative diagnosis, most are treated with surgical resection [485].

Pancreatic lymphoepithelial cysts are more common in men, can occur anywhere in the pancreas, are sharply demarcated from surrounding tissues, and range in size from 1 to 17 cm. Patients are usually middle aged, presenting symptoms include abdominal pain, nausea, vomiting, and diarrhea, although many tumors are asymptomatic and are discovered incidentally on organ imaging or at autopsy. An elevated serum carbohydrate-associated antigen 19-9 may wrongly suggest a mucinous neoplasm. The diagnosis can be made preoperatively with a combination of organ imaging, fine needle aspiration biopsy, or ultrasound-guided Trucut biopsies. Cysts can be unilocular, bilocular, or multilocular, have walls up to 0.6 cm thick which are lined by squamous epithelium, occasional columnar mucinous cells, and small foci of sebaceous cells. The epithelium is surrounded by a dense rim of lymphoid tissue with scattered lymphoid follicles. Invaginations of the epithelium into the lymphoid tissue, reminiscent of a Warthin tumor, are occasionally observed. The pathogenesis is unknown. Pancreatic lymphoepithelial cysts are cured by conservative resection but if they are asymptomatic and are diagnosed before surgery, no treatment is necessary [486].

Mucinous nonneoplastic cyst

Mucinous nonneoplastic cysts (MNCs) are a recently described entity by Kosmahl et al. Microscopically, these cysts are characterized by mucinous differentiation of lining epithelium, lack of cellular atypia or increased proliferation, and a thin rim of supporting, almost acellular, stroma. MNCs need to be differentiated from other mucinous lined epithelial pancreatic cysts, including IPMTs, mucinous cystic neoplasms, and retention cysts. MNCs by definition have no neoplastic features such as dysplasia, invasive growth, or metastatic spread. The underlying cause of MNCs is unknown, but may be due to a developmental defect of the pancreas, resulting in focal cystic transformation of the pancreatic duct. On imaging, they appear as circumscribed unilocular or multilocular fluid collections, which do not communicate with the pancreatic duct. MNCs range in size from 3 to 12 cm and usually occur in the pancreatic head. Mean age of diagnosis in the series by Kosmahl et al was 58 years with no obvious gender predilection. Clinical symptoms if present are nonspecific, including epigastric pain and obstructive jaundice, due to extrinsic compression of the common bile duct [485].

NON-PANCREATIC PERIAMPULLARY TUMORS

Duodenal adenoma

Duodenal adenomas develop in patients with familial adenomatous polyposis, incurring a risk of carcinoma. When this risk is high, surgery is indicated. The choice of surgical treatment can be difficult as evidence-based data are lacking. It was now made a systematic review of the literature on the non-medical management of duodenal lesions arising in the setting of familial adenomatous polyposis. Studies were identified through searching MEDLINE. Studies published between 1965 and 2009 were included. Data regarding number of subjects, complications, length of follow-up, recurrence rate and outcome were extracted. Transduodenal resection does not differ from an endoscopic approach in terms of recurrence. Ampullectomy has limited application as only papillary lesions are amenable to

treatment in this manner. Duodenectomy with pancreas preservation is preferable to pancreaticoduodenectomy unless malignancy is present, or cannot be excluded [487].

Tumors of the papilla of Vater

Although benign ampullary tumors are removed endoscopically, due to their potential to progress to malignant disease, the favored treatment for adenocarcinoma is pancreaticoduodenectomy. It was reviewed one institution's experience in order to identify which patients were at highest risk of disease progression following surgical resection, as well as evaluate whether localized T1 tumors are best treated by pancreaticoduodenectomy. It was retrospectively reviewed 157 patients who presented with an ampullary mass, from 2001 to 2010, and identified 51 with benign adenoma and 106 with adenocarcinoma. Patients with malignant tumors most often presented with larger tumors and jaundice, which alone was predictive of survival (OR = 67). Forty-five percent of patients with pathologically confirmed T1 tumors had positive lymph nodes and median survival was modest at 60 months. Lymph node involvement was predictive of recurrence and decreased survival. It was concluded that patients with malignant tumors often present with jaundice and larger tumors. These findings should warrant suspicion for cancer and expedited preoperative workup. Based on the finding that nearly half the patients with T1 tumors had positive lymph nodes, we recommend pancreaticoduodenectomy for any patient with biopsy proven adenocarcinoma who is a suitable candidate for surgery [488].

In large series, papillary tumors are reported to be mostly represented by adenomas and adenocarcinomas, whereas other histological types are less frequent. In one autopsy series, ampullomas represent approximately 0.2 percent of overall gastrointestinal tract tumors, and the annual age-adjusted incidence of ampullary adenocarcinoma is 0.3 per 100,000 individuals, accounting for 6% of all periampullary tumors. Unexpectedly, carcinomas of the papilla occur more frequently than carcinomas of the small intestine far from the periampullary region. Presently, the histological classification of papillary carcinomas is not sufficiently taken into account to direct the therapeutic assessment. Tumors of the ampulla of Vater are considered, by a surgical point of view, as a uniform entity concerning diagnosis, type of intervention, and prognosis, too often neglecting the role of pathological origin of the tumor. These neoplasms are uncommon and, in large series, are mostly represented by adenomas and adenocarcinomas, whereas other histological types are less frequent. Owing to its peculiar structure that features a junction between 2 different epithelial linings, the ampulla is an interesting area because tumorigenesis may involve two "colliding epithelia." According to morphological and immunohistochemical classification, it may be distinguished pancreaticobiliary-type adenocarcinomas arising from the distal part of ductal pancreatic or biliary epithelium (keratin 7, positive; keratin 20, negative; mucin2 (MUC2), negative; and CDX-2, negative) and intestinal-type adenocarcinomas, originating from the intestinal mucosa lining, the papilla (keratin 7 negative, keratin 20 positive, MUC2 positive, CDX-2 positive). From a histological point of view, the intestinal type is not different from its colonic counterpart, and the same is true for the pancreaticobiliary type compared to pancreatic tumors. Within the adenocarcinomas, an extremely rare histological subtype called signet ring cell carcinoma (SRC) has been described, which is normally found in the gastrointestinal tract, particularly in the stomach, but also described as a ubiquitous variant of adenocarcinoma. Sixteen cases of papillary localization of SRC have been reported in literature. All SRCs previously described had an intestinal-type immunohistochemical pattern. It was now reported a case of a small SRC of the ampulla with a probable origin from the pancreatic biliary epithelium, surgically treated with duodenopancreasectomy with lymphadenectomy [489].

Endoscopic resection of ampullary adenomas

Ampullary adenomas have the potential to progress from benign to malignant lesions. Endoscopic ampullectomy as curative therapy has gained credibility as a safe and effective alternative to surgical resection. One study was designed to assess outcomes of endoscopic resection of ampullary neoplasms at a single center. Between 1996 and 2009, all patients referred to our center for endoscopic resection of an ampullary lesion were retrospectively identified. Patients were followed for complications and endoscopic surveillance performed per protocol to assess for recurrence. Endoscopic ampullectomy for adenoma was performed in 38 patients (22 females; mean age, 54 years, range, 22-85 years), with high-grade dysplasia (HGD) diagnosed in 6 and low-grade dysplasia (LGD) in 32. A direct relationship was observed between HGD and tumor size. Lesions less than 2.5 cm in size demonstrated no evidence of invasion. Mean follow-up duration was 17 ± 2 months (range, 0-83 months). Complications were uniformly mild and occurred in 6 (16 %) patients: bleeding in 2, pancreatitis in 3, and infection in 1. Adenoma recurrence was documented in 6 (16 %) patients, 4 with LGD and 2 with HGD; no patients had tumors that progressed from LGD to HGD or HGD to cancer. Kaplan-Meier analysis showed insignificant differences in recurrence between HGD and LGD groups. Endoscopic ampullectomy is a safe and effective treatment for benign ampullary neoplasms and should become the treatment of choice rather than surgical therapy [490].

OTHER RARE EXOCRINE PANCREATIC TUMORS

Solid pseudopapillary tumor

The objective of one study was to examine the clinicopathologic characteristics of solid pseudopapillary tumors (SPTs) of the pancreas, including the risk factors for disease recurrence and their effects on survival. The medical records of 114 patients who underwent surgery for a pathologically confirmed SPT between 1995 and 2007 were reviewed retrospectively. Of the 114 patients, 98 (87 %) were female, and the median age was 36 years (range, 11-75). All 114 patients underwent curative intent surgery and 13 (11 %) underwent laparoscopic surgery. Of the 114 patients, 26 (23 %) had solid pseudopapillary carcinoma (SPC). There were no differences in any clinical factors between the benign SPT and SPC groups; however, the only 4 recurrences identified were in the SPC group. After follow-up ranging from 11 to 177 months, all 114 patients were alive, with only 4 showing evidence of recurrence. Recurrence was observed in young patients with metastasis at first operation, invasion of an adjacent organ, and a large mass (≥ 13 cm). It was concluded that adequate operative resection including laparoscopic surgery is the mainstay of treatment for SPT. Although statistically significant risk factors for recurrence cannot be determined, tumor metastasis at the first operation, invasion of adjacent organ, large tumor size, young patient age, tumor rupture, and inadequate resection may increase the risk of recurrence. The results demonstrate that long-term survival could be achieved by aggressive operative resection and interventional treatment of recurrent disease [491].

Distinguishing between solid-pseudopapillary neoplasms (SPNs) and pancreatic neuroendocrine tumors (PanNETs) may pose a diagnostic dilemma. Both can demonstrate solid growth patterns, and both can be immunoreactive with neuroendocrine markers such as synaptophysin and CD56. One well-established feature of SPNs is the presence of hyaline globules, which in contrast has only rarely been reported in PanNETs. Clinicopathologic features of 361 cases originally classified as PanNETs were examined. Of these, 24 tumors (7 %) had hyaline globules, raising the possibility of SPN. Immunohistochemistry for β -catenin was performed on these 24 neoplasms, and showed nuclear labeling in 6 cases. These 6 cases, which also demonstrated cytoplasmic CD10 staining, were reclassified as

SPNs. The remaining 18 cases maintained their original diagnosis as PanNETs, and the hyaline globules in these cases were periodic acid-Schiff (PAS) positive, diastase resistant, and immunoreactive with alpha-1-antitrypsin. All 24 cases were histologically re-evaluated, and the pattern of invasion, presence of clear cells, and nuclear grooves were found to be helpful in distinguishing SPNs from PanNETs. We conclude that the presence of hyaline globules should raise SPNs in the differential diagnosis of a solid cellular neoplasm of the pancreas. However, this should not be used as the sole criterion in the diagnosis of SPNs, as hyaline globules may also be seen in 5 percent of PanNETs. Immunohistochemical and histologic features supporting the diagnosis of SPNs over PanNETs include CD10 and nuclear beta-catenin labeling, an insidious pattern of invasion, clear cells, and nuclear grooves [492].

The aim was to summarize our experience with the diagnosis and surgical treatment of solid pseudopapillary neoplasm (SPN) of the pancreas to provide a reference for the management of this rare condition. It was collected and analyzed retrospective data on the clinical presentation, laboratory investigations, radiologic imaging, pathology and operative details of patients with SPN of the pancreas diagnosed between 2001 and 2009. In all, 23 of 24 patients were women, and the mean age of all patients was 31 years. The most common clinical presentation was vague abdominal pain. Abdominal imaging showed solid or solid cystic masses in the pancreas, mostly in the tail or head of the gland. All patients were treated surgically. There were no postoperative deaths. After follow-up ranging from 4 to 109 months (median 68 mo), 20 of 22 patients who underwent curative resection were alive with no evidence of disease recurrence. Of the 2 patients with R1 resections, 1 died 42 months after surgery, whereas the other underwent a second operation and was alive after 36 months' follow-up. Solid pseudopapillary neoplasm of the pancreas is a relatively indolent tumour. The initial diagnosis of SPN of the pancreas is suggested by radiologic imaging findings but should be considered in the context of clinical and histopathologic characteristics. It was advocate for complete surgical resection once SPN is diagnosed [493].

CD99

The aim of one study was to investigate CD99 as a new marker to characterize solid pseudopapillary tumors (SPTs), and to determine a specific panel of markers to identify the disease. It was analyzed the clinicopathological characteristics and immunohistochemical features of 37 patients with SPT. All 37 tumors displayed intracytoplasmic dot-like immunoreactivity of CD99 in contrast to membranous staining in all pancreatic endocrine tumors and most of acinar cell carcinomas, along with negative immunostaining in ductal carcinomas. In addition, we observed a loss of expression of E-cadherin in all SPTs as well as in some other pancreatic tumors, and aberrant nuclear expression of beta-catenin in most SPTs. Our findings demonstrated for the first time that the pattern of CD99 expression was highly specific for distinguishing SPTs from other pancreatic tumors. CD99 combined with E-cadherin/beta-catenin and CD10 can be used as a relatively specific expression profile of SPTs [494].

Acinar cell carcinoma

Acinar cell carcinoma (ACC) of the pancreas is characterized by better long-term survival compared with the more common ductal adenocarcinoma, and prognosis is better in resected compared with nonresected patients. The aim of one study was to investigate the role of surgery in ACC with limited metastatic disease. All patients with histologically confirmed ACC treated at the investigators' institution between 2001 and 2009 were identified from a prospective database. Clinicopathologic details, perioperative results, and follow-up results were analyzed. Seventeen patients with nonmetastatic and metastatic ACC

were identified. Initially, localized, locoregional, and metastatic disease was present in 5, 7, and 5 patients, respectively. Pancreatic resections were performed in 15 patients. In limited metastatic disease, additional liver resection was performed in 3 patients and omentectomy in 1 patient. In 2 patients, metachronous liver metastases were resected. With a median follow-up period of 37 months, overall 1-year, 2-year, and 3-year survival rates were 88 percent, 65 percent, and 47 percent, respectively. Survival of resected patients with metastatic and nonmetastatic disease showed no differences between the 2 groups. It was concluded that ACC of the pancreas is a relatively rare tumor entity for which resection may result in long-term survival even in limited metastatic disease [495].

Acinar cell carcinoma (ACC) is a rare pancreatic tumour with a favourable prognosis compared with the more common ductal adenocarcinoma. The radiological findings of this tumour have been described in the literature; however, only limited data are available regarding the metastatic features of ACC of the liver, the most common metastatic site. It was reported a case of ACC of the pancreas with a hepatic metastasis from a benign-appearing malignant pancreatic lesion [496].

Acinar cell carcinoma of the pancreas is a rare malignant tumour developing from acinar cells, accounting for approximately 1 percent of pancreatic exocrine tumours. It was experienced a case of an acinar cell carcinoma with fatty change. It was the first case report of an acinar cell carcinoma with fatty change in the clinical literature [497].

Spindle cell tumors

The role of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in the evaluation of spindle cell and mesenchymal lesions is unclear. One study reviewed the use of EUS-FNA in diagnosing intrathoracic and intra-abdominal spindle and mesenchymal cell lesions at an academic institution. All EUS-FNA specimens with a significant spindle or mesenchymal cell component were retrieved. Follow-up was comprised of clinical correlation, chart review, or evaluation of subsequent tissue specimens, including FNAs, biopsies, and/or surgical resections. Lesions were categorized as either inflammatory/reactive or neoplastic. Forty-four EUS-FNA specimens were retrieved from 39 patients (21 men and 18 women with a median age of 61 years). Anatomic sites included 19 lymph node specimens, 15 gastrointestinal tract specimens, 7 pancreatic specimens, and 4 other anatomic site specimens. Twenty-two cases were inflammatory/reactive lesions, including 17 granulomatous lesions and 5 cases of chronic pancreatitis. Twenty-two cases were neoplastic, including 14 gastrointestinal stromal tumors, 2 smooth muscle tumors, 2 sarcomatoid carcinomas, 2 melanomas, 1 sarcoma, and 1 solitary fibrous tumor. A specific cytologic diagnosis was rendered in 30 cases (81%). Immunocytochemistry was performed on 21 neoplastic cases and contributed to the differential diagnosis in 18 cases. No false-positive findings were encountered. Three false-negative results were identified and were attributed to sampling error. It was concluded that spindle cell neoplasms are rarely encountered on EUS-FNA. The differential diagnosis encompasses a wide variety of benign and neoplastic entities. Correlation of cytomorphology and ancillary studies yields a high diagnostic accuracy of spindle cell and mesenchymal lesions on EUS-FNA [498].

Mixed ductal-endocrine carcinoma

A metastatic mixed endocrine-ductal carcinoma of the liver was discovered in a 71-year-old woman during attempted distal pancreatectomy for an endocrine neoplasm diagnosed by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Contrast-enhanced computed tomographic (CT) scan 87 days earlier showed no liver lesions. The short interval

of metastatic seeding supports the highly aggressive behavior of mixed carcinomas and justifies management akin to conventional ductal adenocarcinoma. In hindsight, a malignant ductal component admixed with gastrointestinal contaminants and neoplastic endocrine cells verified the pancreatic lesion as the primary. Thereby, it was pointed out a rare diagnostic dilemma in the preoperative management and treatment stratification of patients with pancreatic endocrine neoplasms. Given the predominant endocrine component, the liver lesion is diagnostic of a metastasis from the pancreatic primary with divergent cellular differentiation indicative of a common tumor precursor stemcell. The presence of a mixed ductal and endocrine metastasis from a pure endocrine neoplasm has only been reported once previously. The case is remarkable for several reasons. First, it outlines how cytopathologic classification into endocrine versus exocrine neoplasms on FNA is translated into clinical management. Specifically, given the negative metastatic workup and nonfunctioning endocrine neoplasm diagnosed by FNA, a distal pancreatectomy was planned. Second, the liver metastasis found during exploratory laparotomy likely developed during the 87 days after the detection of the pancreatic mass because imaging 10 days after the operation clearly demonstrated at least 15 enhancing lesions (Fig. 1H). This rapid metastatic spread supports an overall aggressive biologic behavior of the carcinoma. Third, histopathologic findings in the liver metastasis triggered a review of the original FNA, which revealed a malignant glandular component, changing the preoperative diagnosis from endocrine neoplasm to mixed ductal and endocrine carcinoma of the pancreas, a diagnosis that, in this case, with imaging consistent with a T4 stage, would have led to neoadjuvant therapy rather than surgery. Thus, recognition of a ductal carcinoma component (admixed with an endocrine neoplasm and possibly gastrointestinal contaminants) in the limited FNA sample has serious management implications [499].

Osteoclastic giant cell tumor

Giant cell tumors of the pancreas are rare neoplasms divided into three forms: osteoclastic, pleomorphic, and mixed. It was reported an unusual case of a 62-year-old male presenting with recurrent acute pancreatitis and found to have a mass in the head of the pancreas on routine imaging. Endoscopic retrograde cholangiopancreatography showed a main pancreatic duct stricture, with brush cytology revealing the diagnosis of osteoclastic giant cell tumor of the pancreas. Whipple's procedure was successfully performed for resection of this tumor [500].

Anaplastic cancer

Anaplastic pancreatic cancers are rare neoplasms. The available data are focused on pathologic and molecular features, and little is known about the clinical presentation and management. The outcome of operative exploration and resection is unknown. From a prospective database, all consecutive operations for anaplastic pancreatic cancer performed at our institution were identified. The clinicopathologic details were analyzed and the outcome was compared with a matched group of typical pancreatic ductal adenocarcinomas (nested case-control study). Eighteen patients with anaplastic pancreatic cancer were identified. The patients had a median age of 64 years. The tumors were large (median diameter, 4 cm) and showed peripheral contrast enhancement in radiologic imaging. Fifteen (83 %) patients underwent resection, a palliative bypass procedure was performed in 1 (6 %) patient, and 2 patients underwent exploration with biopsy only. Perioperative morbidity was 39 percent and mortality was 6 percent. The median survival rate in patients with anaplastic pancreatic cancer was 6 months and was less than in the control group of patients with pancreatic ductal adenocarcinoma (16 months). In anaplastic pancreatic cancer, the median duration of survival was significantly greater after R0/R1 resection, as compared with

palliative surgery (7 vs 2 months). The duration of survival was significantly greater in neoplasms with osteoclast-like giant cells. In 3 (17 %) patients, long-term survival of 33, 49, and 161 months was observed. It was concluded that anaplastic pancreatic cancer is an aggressive type of pancreatic cancer with a short median survival; however, because of the observation of prolonged survival after resection, resection should be performed whenever possible. The presence of osteoclast-like giant cells is associated with a favorable prognosis [501].

Mucinous adenocarcinoma

Mucinous adenocarcinomas (MAs) of various origins may have a similar histologic appearance and frequently metastasize to distant sites, which often causes diagnostic problems in surgical pathology practice. The immunohistochemical profiles of MAs of various origins have not been well studied. It was investigated the expression of 10 immunohistochemical markers (CK7, CK20, CDX-2, β -catenin, MUC-1, MUC-2, MUC-6, ER, WT-1, and PAX-8) in 175 cases of MA, including 69 cases from the lower gastrointestinal (GI) tract, 41 from the upper GI tract, 27 from gynecologic organs, 4 from the urinary bladder, 18 from the breast, and 16 from the lung. It was found that lower GI MAs (colon, rectum, and anus) frequently expressed CDX-2 (42 of 42, 100 %; 33 of 42 with homogenous positivity, 79 %), MUC-2 (42 of 42; 100 %), CK20 (41 of 42; 98%), and beta-catenin (nuclear) (27 of 42; 64 %) and rarely expressed MUC-6 (2 of 42; 5 %) and CK7 (8 of 42; 19 %). Most of the CK7-positive cases were from the rectum and anus (7 of 8; 88 %). The expression of these markers in appendiceal MAs was similar to that of low GI tract MAs, except for a lower percentage of homogenous CDX-2 (3 of 27; 11 %) and nuclear beta-catenin (3 of 27; 11 %) expression. Unlike their lower GI tract counterparts, the upper GI tract MAs (ampulla, pancreas/biliary tree, and stomach/esophagus) frequently expressed CK7 (38 of 41; 93 %) and MUC-6 (31 of 41; 76 %) and were rarely homogeneously positive for CDX-2 (4 of 41; 10 %) and nuclear positive for beta-catenin (8 of 41; 19 %). Breast MAs were frequently positive for CK7 (18 of 18; 100 %), MUC-1 (18 of 18; 100 %), MUC-2 (18 of 18; 100 %), ER (16 of 18; 89 %), MUC-6 (9 of 18; 50 %), and WT-1 (9 of 18; 50 %). Lung MAs were frequently positive for CK7 (16 of 16; 100 %) and MUC-1 (15 of 16; 94 %). Gynecologic MAs were positive for CK7 (25 of 27; 93 %) and PAX-8 (13 of 27; 48 %). It was concluded that homogenous CDX-2 and nuclear beta-catenin expressions are commonly seen in lower GI tract MAs. In contrast, appendiceal MAs are usually heterogeneously positive for CDX-2 and show cytoplasmic positivity for β -catenin. Unlike lower GI tract MAs, upper GI tract MAs are frequently positive for CK7 and MUC-6. As is the case in appendiceal MAs, the upper GI tract MAs may also be heterogeneously positive for CDX-2. Breast MAs are positive for ER and WT-1, whereas gynecologic MAs are positive for PAX-8 and negative for WT-1 [502].

PEComa

There is one report of a perivascular epithelioid cell neoplasm (PEComa) originating from the pancreas and metastasizing to the liver [503].

Lymphoma

It was reported a primary pancreatic lymphoma as a rare cause of massive upper gastrointestinal hemorrhage [504].

B-cell lymphoma

Pancreatic lymphoma is uncommon, representing less than 0.5 percent of pancreatic tumors, with diffuse large B-cell lymphoma being the predominant histotype. Acute pancreatitis associated with pancreatic lymphoma is rare. It was described a case of synchronous pancreatic and pulmonary localizations of non-Hodgkin's lymphoma in a 42-year-old man who presented with acute pancreatitis. Acute pancreatitis resolved after standard treatment with a fasting regimen, gabexate mesilate and parenteral nutrition. However, ultrasound scan and abdominal computed tomography revealed two hypoechogenic areas within the pancreas, and chest X-ray film showed a pulmonary infiltrate in the right basal field. A percutaneous fine-needle aspiration biopsy of the pulmonary infiltrate under computed tomography guidance demonstrated a diffuse infiltration by atypical lymphoid cells positive for leukocyte common antigen, CD20 and CD30. Percutaneous fine-needle aspiration biopsy under ultrasound guidance of the pancreatic mass confirmed the diagnosis of diffuse large B-cell lymphoma. The patient was classified as stage IV-A, low-intermediate risk and received 6 cycles of chemotherapy. This is the first case of large B-cell lymphoma presenting with concomitant primary pancreatic and pulmonary involvement. Pancreatic lymphoma is uncommon and represents a rare cause of acute pancreatitis. The discovery of a pancreatic mass needs pathologic diagnosis to distinguish lymphoma from carcinoma or autoimmune pancreatitis [505].

Pancreatic tumors in children

Pancreatic neoplasms are rare in children and adolescents; thus, the understanding of these tumors is still quite limited. It was retrospectively reviewed clinical features and outcomes of all patients below 18 years of age with pancreatic neoplasms who were treated 1994 to 2010. Thirty-two patients were identified. Abdominal pain was the most common symptom. The median duration of diagnostic delay was 21 days. Nineteen patients were diagnosed with solid pseudopapillary tumors, 3 with lymphomas, 2 with pancreatoblastomas, 2 with poorly differentiated carcinomas, 2 with acinar cell cancers, 2 with endocrine tumors, 1 with peripheral (primitive) neuroectodermal tumor, and 1 with hemangioendothelioma. Gross complete resection of the primary tumor was achieved in 24 patients (75 %), and 8 patients (25 %) received chemotherapy. At a median follow-up of 34 months, the 5-year overall survival rate was 92.± 6 %. On multivariate analysis, histologic type was the only factor significantly predictive of survival. Patients with poorly differentiated carcinoma showed the worst survival probability. In cases of solid pseudopapillary tumors, surgical resection was generally curative and the prognosis was excellent. Patients with other malignant tumors, however, may require therapeutic strategies other than surgery [506].

Haemangioendotheliomatosis

Primary pancreatic tumors are extremely rare in children. It was reported a case of a 5-month-old male with a diffuse invasive tumour of the head of the pancreas. The tumour demonstrated peripancreatic extension into the porta hepatis, which occluded the portal vein and invaded the superior mesenteric artery. It was found to be haemangioendotheliomatosis of the pancreas [507].

Pancreatoblastoma

Pancreatoblastoma is a very rare malignant tumour typically occurring in the early years of life. Due to its rarity, standardised diagnostic and therapeutic guidelines are not available for pancreatoblastoma. The newborn cooperative group denominated EXPeRT – European cooperative study group for paediatric rare tumours – combined in a joint analysis of all

cases registered between 2000 and 2009 by the national groups of Italy, France, United Kingdom, Poland and Germany. Twenty patients <18 years old (median age 4 years) were analysed: nine had distant metastases at diagnosis. Seventeen patients had tumour resection, at initial or delayed surgery. Eighteen received chemotherapy (response rate 73 %), seven received radiotherapy. For the whole series, 5-year event-free survival and overall survival were 59 percent and 79 percent, respectively. Outcome did not correlate with tumour site and size, but was strongly influenced by the feasibility of tumour complete resection. This international study confirms the rarity of the disease, the critical role of surgical resection both as therapy and as a prognostic variable, and the potential efficacy of chemotherapy. The adoption of an intensive multidisciplinary approach is required, as well as the referral to highly experienced centres. Further international cooperation is needed to collect larger series and stimulate biological studies to improve our understanding of the biology and the natural history of PBL [508].

Desmoplastic fibroblastoma

Desmoplastic fibroblastoma (DF), also known as collagenous fibroma, is a fibrous soft tissue tumor that was first described by Evans in 1995. It was adopted in the World Health Organization classification of soft tissue and bone tumors in 2002. Desmoplastic fibroblastoma is a benign tumor that is generally well circumscribed and consists of spindle cells, with features of fibroblast/myofibroblasts, interrupted by collagenous stroma. The tumor presents as a slowgrowing painless mass. It has a wide anatomical distribution but typically arises in the subcutaneous tissue or skeletal muscle. Desmoplastic fibroblastoma usually emerges in the fifth or sixth decade of life, predominantly in men. Surgery is the treatment of choice for DF tumors, with no reported tumor recurrence or metastases. It was now described a DF involving the pancreas, the first such case to be reported in the literature to our knowledge. Immunohistochemically, the spindle tumor cells demonstrated strong and diffuse expression of vimentin. Some of the cells had a myofibroblastic immunophenotype as demonstrated by focal reactivity for smooth muscle actin. The tumor tissue was not immunoreactive for CD34, Factor13, anaplastic lymphoma kinase, S100 protein, or desmin. Based on these findings, the tumor was diagnosed to be a DF. The present report describes a case of DF in the tail of the pancreas with strong vimentin expression and focal smooth muscle actin immunoreactivity, features that are indicative of a fibroblasticmyofibroblastic mass identity. The size of the tumor in this case (4.5 cm in diameter) was similar to prior DF tumors, which typically range in diameter from 1 to 20 cm, with a median diameter of 3 cm. Desmoplastic fibroblastoma tumor cells are generally focally positive for vimentin but not for desmin or CD341 as was observed in this case, and rarely may be positive for keratins. Dystrophic calcification and metaplastic bone have been described in some prior DF cases. Surgical resection is indicated in low-risk patients in whom pancreatic masses are found and for whom a diagnosis of serous cystadenoma has been definitively ruled out. Whereas DF pathogenesis has not been clarified, previous cytogenetic studies have revealed clonal chromosome abnormalities involving the 11q12 breakpoint, supporting the neoplastic nature of DFs. The differential diagnosis for a suspected DF includes a variety of fibroblastic lesions, most notably fibromatosis, low-grade fibromyxoid sarcoma, solitary fibrous tumor, calcifying fibrous pseudotumor, neurilemmoma, myofibroblastic sarcoma, inflammatory myofibroblastic tumor, and gastrointestinal stromal tumor. These diagnoses can be excluded when a mass presents with a well-circumscribed nature, hypocellularity, an absence of mitotic activity and atypia, an absence of lymphoplasmacytic infiltration, and negative immunoreactivity for CD34 and anaplastic lymphoma kinase. In summary, when a soft tissue mass is discovered in the pancreas, the physician should consider DF as a possible diagnosis given that the present case demonstrates that a pancreatic DF is possible, albeit rare. Such consideration may prevent misdiagnosis that could lead to inappropriate treatment and determination of prognosis [509].

Hemangioma

Haemangiomas are common benign tumours that are generally detected within the skin, mucosal surfaces and soft tissues. However, intranodal haemangiomas are extremely rare and are among the benign primary vascular abnormalities of the lymph nodes that include lymphangioma, haemangioendothelioma, angiomyomatous hamartoma and haemangiomas. In this case report, we present the imaging and pathological findings of an intranodal haemangioma in the pancreatic head simulating a pancreatic neuroendocrine tumour. To the best of our knowledge, this is the first report of an intranodal haemangioma in this location [510].

Cholesterol granuloma

Cholesterol granuloma (CG) is pathologically characterized by an inflammatory reaction to the by-products of hemoglobin degradation present in an extravascular compartment. Cholesterol granuloma commonly involves the head and neck, particularly the middle ear and cranial bones, but cases of CG in other locations, such as breast, peritoneum, and kidney, have rarely been reported. Granulomas of the pancreas seem rare and include infectious granuloma, pancreatic involvement in systemic granulomatous disease, foreign body granuloma due to previous surgical operations, and granuloma with chronic pancreatitis. It was now reported a surgical case of huge cholesterol granuloma in the pancreas accompanied by peritoneal disseminated lesions. Although CGs are extremely rare in the pancreas and the details of the pathogenesis are unclear, several theories about the pathogenesis of cholesterol granuloma have been proposed, including local hemorrhage occurring during an inflammatory process, obstruction of ventilation, and poor drainage. Similar pathogeneses may be applicable to pancreatic CGs and pancreatitis-induced local hemorrhage, extravascular leakage of blood, and inflammatory reaction would be necessary for CG formation. Although CGs in the pancreas form in precious few patients with acute pancreatitis and some mechanisms remain unrecognized, pancreatic CGs should be classified into the subtype of inflammatory pseudocysts [511].

Metastases to the pancreas

Metastasis from cervix uteri

Pancreatic metastases from various primary cancers have been reported, accounting for approximately 2 percent of pancreatic malignancies. Although most pancreatic metastases occur in conjunction with widespread disease, isolated metastases are sometimes found. At least 40% of these isolated metastases originate from renal cell carcinoma; other common primary sites include the lung, breast, and colon as well as melanoma and sarcoma. Pancreatic metastasis from uterine cervical cancer seems to be very rare, and only three cases have been reported to date. Now one more case was presented [512].

Metastases from renal cancer

Late recurrence is one of the specific biologic behaviors of RCC; however, the clinical and pathologic features of the late recurrence of RCC are not fully understood. To evaluate in collaboration the clinical features of late recurrence of renal cell carcinoma (RCC) a total of 470 patients who had undergone curative treatment of RCC and had not developed recurrence within 10 years of follow-up were documented from 13 institutions of the board members of the Japanese Society of Renal Cancer. Multivariate analysis with Cox

proportional hazards model was used to determine the pathologic and clinical factors affecting the late recurrence and survival of patients with RCC ≥ 10 years after surgery. During the 10-28-year (median 13) observation period, 30 patients (6 %) developed a late recurrence. The disease-free survival rate at 15 and 20 years was 90 percent and 78 percent, respectively. Multivariate analysis showed that lymph node metastasis was the only factor to predict for late recurrence. Age at nephrectomy was the only prognostic factor for overall survival on multivariate analysis. Of the 470 patients, 30 had developed late recurrence in 44 sites, including the lung (36 %), kidney (25 %), and bone (14 %), followed by the brain, pancreas, adrenal gland, lymph nodes, and liver. Late recurrences in the lung or kidney were observed at any time ≥ 10 years after nephrectomy. It was concluded that late recurrence of RCC after initial treatment is not a rare event, and lifelong follow-up is necessary [513].

Metastases from the breast

It was reported a case of pancreatic metastasis from breast cancer during multimodality therapy. A 53-year-old woman received right breast-conserving surgery for invasive ductal carcinoma and then chemo-radiotherapy for liver, brain, bone, neck and axillary lymphnodes, mediastinum, pleural, and spinal cord metastasis. Although she then survived in a tumor-free condition, a blood examination performed 4 years after the surgery showed an elevated serum amylase level. Abdominal CT and US revealed swelling of the pancreas head and body with main pancreatic duct dilatation of the pancreatic tail. ERCP showed diffuse stenosis of the extrahepatic bile duct and the main pancreatic duct of the pancreatic head and body. Immunohistochemical staining of the biopsy specimen from the pancreatic head confirmed pancreatic metastasis from breast cancer. Despite the intensive chemotherapy including trastuzumab, she died two years after the onset of pancreatic metastasis. Metastatic breast cancer to the pancreas is very rare. However, considering the recent advances of multimodality therapy for breast cancer, this clinical state may become more common [514].

Metastases from prostate

It was reported a case where FDG PET/CT demonstrated a pancreatic metastasis from prostate cancer [515].

Metastases from pancreatic cancers

In the United States, a 3-fold increase of pancreatic cancer was noted between 1920 and 1978. In Hungary, however, the mortality rate has increased by 16-fold during the last 60 years (1948: 1.1/100,000, 2008: 18/100,000), accounting for the highest rise in Europe. Therefore, it was investigated the main clinicopathologic features and the metastatic pattern of this tumor during a 60-year period in an autopsy material. The autopsy reports between 1947 and 2006 of the First Department of Pathology and Experimental Cancer Research, Semmelweis University in Budapest, have been surveyed and analyzed for decades. Only the histologically proven ductal adenocarcinomas have been assessed; the endocrine and cystic neoplasms were excluded. In the 60-year autopsy material, 426 pancreatic adenocarcinomas were found (223 men, 203 women). The number of cases has increased by decades: 56 cases in the first decade (between 1947 and 1956), 62 in the second, 55 in the third, 71 in the fourth, 74 in the fifth, and 108 cases in the last analyzed decade (1997 to 2006). Their increasing number well reflects the general mortality rates in Hungary. The average patient age was 67 years, with no significant differences between men and women. Most of the tumors (60 %) were located in the pancreatic head, followed by the body and the tail. Regarding the carcinomas of the body, their proportion has decreased from 20% to 10%

in the last 30 years. Up to 9% of cases, the tumor has infiltrated the whole organ (diffuse form), making impossible to determine the exact site of the origin. The radical operations showed an increased tendency; however, it was only 5.6 percent in the last decade. Palliative surgical intervention has become more frequent (from 20 % to 44 %), but because of the advanced tumorous diseases, the supportive care remained the major treatment modality. Obstructive jaundice was diagnosed in 76 percent of the head tumors. Marantic, nonbacterial endocarditis was rarely recorded (10 cases, 2 %), but venous thromboses and/or thromboemboli were found in 33 percent (141 cases). Among them, there were just 19 splenic vein thromboses; the rest developed in the iliac/femoral veins. It was found that the most frequent cause of death was unrelated to the cancer (76 %), whereas the tumorous and tumorrelated deaths occurred almost equally (12 % and 12 %, respectively). Rarely, pancreatic cancer was accompanied by synchronous primary malignancies (23 cases, 5 %), but their anatomic distribution was highly variable. Metastases were found in 357 cases (84 %); the tumor remained localized in 69 patients. In other words, in the majority of cases, stage IV tumors were found, and the proportion of this advanced carcinomas has increased in the last decades. Regional lymph node metastases occurred in 57 percent (242 cases). The distant lymph nodes (including Virchow node) were rarely involved (6 %). As for the secondarily affected distant organs, a wide variety was observed. Metastases were found in the liver (261 cases, 61 %), on the peritoneum (101 cases, 24 %, accompanied by ascites in one third of carcinosis), in the lungs and on the pleural surface (94 cases, 22 %), in the adrenals (5 %), in the bones (5 %), in the kidneys (4 %), in the heart (3 %), in the gallbladder (3 %), in the spleen (2 %), in the diaphragm (2 %), and in the brain (1 %). Other, unusual metastatic sites were the stomach, thyroid gland, ovary, prostate, epididymis, esophagus, rectum, ureter, abdominal wall, colon, or the breast. The body and tail tumors behaved more aggressively: both the liver and, generally, the organ metastases were significantly more frequently found than those originating from the carcinomas of the head [516].

Ovarian metastases

Metastatic mucinous carcinomas in the ovary are readily recognized when they show characteristic features, including bilateral involvement, only moderate tumor size, surface and superficial cortical involvement, nodular growth, and an infiltrative pattern. However, it is well established that some metastatic mucinous carcinomas can simulate primary ovarian mucinous tumors grossly and microscopically. Metastatic pancreaticobiliary tract adenocarcinomas present a particular diagnostic challenge due to their ability to exhibit borderline-like and cystadenomatous growth patterns, which can be misinterpreted as underlying primary ovarian precursor tumors and can be erroneously used to support interpretation of the carcinomatous components as arising from these purported precursors within the ovary. Thirty-five cases of metastatic pancreaticobiliary tract adenocarcinomas were analyzed. The mean patient age was 58 years (median, 59 y; range, 33 to 78 y). In 15 cases (43 %), the pancreaticobiliary tract and ovarian tumors presented synchronously and in 2 cases (6 %) the ovarian tumors presented earlier as the first manifestation of the disease. Ovarian tumors were bilateral in 31 cases (89 %). Mean and median tumor sizes were 111 and 10 cm, respectively (range, 3 to 21.0 cm). Nodularity was present in 22 cases (63 %) and surface involvement was identified in 14 cases (40 %). An infiltrative growth pattern was present at least focally in 28 cases (80 %), accompanied by borderline-like and/or cystadenomatous areas in 17 (49 %) cases and as the exclusive pattern in 11 cases (31 %). Conversely, borderline-like and cystadenomatous patterns were identified in 24 cases (69 %) and as the exclusive patterns (either pure or combined with one another) in 7 cases (20 %). Dpc4 expression was lost in 20 of 33 tumors analyzed (61 %). Of 25 patients with follow-up, 23 patients had died of disease (mean/median time, 9/6 mo; range, 1 to 39) and 2 patients were alive with disease (at 1 and 25 mo). Frequent bilateral ovarian involvement, moderate tumor size, nodularity, and infiltrative patterns are useful features for identifying these ovarian tumors as metastatic. However, many tumors exhibit borderline-like and cystadenomatous patterns that, when dominant and combined with synchronous

presentation, make recognition as metastases an ongoing challenge. Loss of Dpc4 expression provides the most useful immunohistochemical evidence for establishing the pancreaticobiliary tract as the most likely source of these metastatic mucinous carcinomas in the ovary [517].

Brain metastases

Metastatic brain tumors represent 20 to 40 percent of all intracranial neoplasms and are found most frequently in association with lung cancer (50 %) and breast cancer (12 %). Although brain metastases occur in <4 percent of all tumors of the gastrointestinal (GI) tract, the incidence of GI brain metastasis is rising in part due to more effective systemic treatments and prolonged survival of patients with GI cancer. Data were collected from 25 studies (11 colorectal, 7 esophageal, 2 gastric, 1 pancreatic, 1 intestinal, 3 all-inclusive GI tract cancer) and 13 case reports (4 pancreatic, 4 gallbladder, and 5 small bowel cancer). Brain metastases are found in 1 percent of colorectal cancer, 1.2 percent of esophageal cancer, 0.62 percent of gastric cancer, and 0.33 percent of pancreatic cancer cases. Surgical resection with whole brain radiation therapy (WBRT) has been associated with the longest median survival (38-262 weeks) compared with surgery alone (16-71 weeks), stereotactic radiosurgery (20-38 weeks), WBRT alone (7-16 weeks), or steroids (4-7 weeks). Survival in patients with brain metastasis from GI cancer was found to be diminished compared with metastases arising from the breast, lung, or kidney. Prolonged survival and improvement in clinical symptoms has been found to be best achieved with surgical resection and WBRT. Although early treatment has been linked to prolonged survival and improved quality of life, brain metastases represent a late manifestation of GI cancers and remain an ominous sign [518].

Testes metastases

It was presented a man with a testicular mass and a colon stenosis where the diagnosis was metastatic pancreatic adenocarcinoma to the gonads [519].

PANCREATIC ENDOCRINE TUMORS

Molecular biology

It was recently identified the transcription factor (TF) islet 1 gene product (ISL1) as a marker for well-differentiated pancreatic neuroendocrine tumors (P-NETs). In order to better understand the expression of the four TFs, ISL1, pancreatico-duodenal homeobox 1 gene product (PDX1), neurogenin 3 gene product (NGN3), and CDX-2 homeobox gene product (CDX2), that mainly govern the development and differentiation of the pancreas and duodenum, it was studied their expression in hormonally defined P-NETs and duodenal (D-) NETs. Thirty-six P-NETs and 14 D-NETs were immunostained with antibodies against the four pancreatic hormones, gastrin, serotonin, calcitonin, ISL1, PDX1, NGN3, and CDX2. The TF expression pattern of each case was correlated with the tumor's hormonal profile. Insulin-positive NETs expressed only ISL1 (10/10) and PDX1 (9/10). Glucagon-positive tumors expressed ISL1 (7/7) and were almost negative for the other TFs. Gastrin-positive NETs, whether of duodenal or pancreatic origin, frequently expressed PDX1 (17/18), ISL1 (14/18), and NGN3 (14/18). CDX2 was mainly found in the gastrin-positive P-NETs (5/8) and rarely in the D-NETs (1/10). Somatostatin-positive NETs, whether duodenal or pancreatic in origin, expressed ISL1 (9/9), PDX1 (3/9), and NGN3 (3/9). The remaining tumors showed labeling for ISL1 in addition to NGN3. There was no association between a particular TF pattern and NET features such as grade, size, location, presence of metastases, and functional activity. We conclude from our data that there is a correlation between TF expression patterns and

certain hormonally defined P-NET and D-NET types, suggesting that most of the tumor types originate from embryologically determined precursor cells. The observed TF signatures do not allow us to distinguish P-NETs from D-NETs [520].

TNM classification

To evaluate the prognostic significance of TNM and grading categories in curatively resected non-functioning neuroendocrine pancreatic carcinoma (nfnePC). Eighteen nfnePC were retrospectively analyzed for differences in survival. There was a correlation between pT, respectively pM categories and survival. G categories and length of survival were closely correlated. Disease stages I-IV had a significant effect on survival. The WHO classification in well and poorly differentiated carcinomas proved to be the most conclusive predictive factor. Subgroups with significantly different prognoses determined by histological grade were present within disease stage II. The retrospective analysis showed a good correlation between survival and pT, pM, tumor stage, G categories, and WHO classification in well and poorly differentiated carcinomas. Including histological differentiation in the staging system or carrying it out separately in well and poorly differentiated carcinomas, could enhance the predictive potential of TNM-based disease stages [521].

The American Joint Committee on Cancer (AJCC) staging manual (seventh edition) has introduced its first TNM staging classification for pancreatic neuroendocrine tumors (NETs) derived from the staging algorithm for exocrine pancreatic adenocarcinomas. This classification has not yet been validated. Patients with pancreatic NETs treated between 1999 and 2010 were assigned a stage (I to IV) based on the new AJCC classification. Kaplan-Meier analyses for overall survival (OS) were performed based on age, race, histologic grade, incidental diagnosis, and TNM staging (European Neuroendocrine Tumors Society, ENETS, vs AJCC) using log-rank tests. Survival time was measured from time of initial diagnosis to date of last contact or date of death. Multivariate modeling was performed using Cox proportional hazards regression. Weighted Cohen's κ coefficient was computed to evaluate the agreement of ENETS and AJCC classifications. It was identified 425 patients with pancreatic NETs. On the basis of histopathologic grade, 5-year survival rates for low-, intermediate-, and high-grade tumors were 75 percent, 62 percent, and 7 percent, respectively. When using the ENETS classification, 5-year OS rates for stages I, II, III, and IV were 100 percent, 88 percent, 85 percent, and 57 percent, respectively. Subsequently, using the AJCC classification, 5-year OS rates for stages I, II, III, and IV were 92 percent, 84 percent, 81 percent, and 57 percent, respectively. Both the novel AJCC classification and the ENETS classification were highly prognostic for survival. The AJCC TNM classification for pancreatic NETs is prognostic for OS and can be adopted in clinical practice [522].

Prognostic factors

Pancreatic neuroendocrine tumors (PNETs) are uncommon malignancies. The purpose of this study was to identify the prognostic factors of pancreatic neuroendocrine tumors at a single center. Clinical data of 27 patients with PNETs treated between 1995 and 2010 were retrospectively reviewed. Survival was estimated with the Kaplan-Meier methodology. Twenty-three patients (86 %) had nonfunctional tumors and four patients (15 %) had functional tumors. The majority of PNETs located in the body and/or tail of the pancreas in 20 patients (74 %). All patients with functional tumors cause syndromes related to hormone overproduction. Anorexia, nausea, vomiting, obstructive jaundice, weight loss, and incidental mass were more common in patients with nonfunctional tumors. The median follow-up time was 40 months. The overall 1-, 2-, and 5-year accumulative survival rates were 91, 81, and 81 percent, respectively. In univariate analysis, factors associating with significantly better

survival included macroscopically radical resection of the primary tumor, tumor-node-metastasis (TNM) staging, World Health Organization (WHO) classification, and palliative chemotherapy. Macroscopically radical resection of the primary tumor, TNM staging, WHO classification, and palliative chemotherapy were prognostic variables which may emerge as a practical clinical tool to predict survival [523].

Glucagonoma

It was reported on a glucagon cell adenomatosis associated with necrolytic migratory erythema and glucagonoma syndrome [524].

Gastrinomas

Gastrinomas, a rare group of neuroendocrine tumors, are responsible for severe peptic disease and diarrhea. Although symptomatic control may be achieved with proton-pump inhibitors (PPIs) and somatostatin analogues (SSAs), data are limited regarding the possible antitumor effect of the peptide receptor radioligand therapy (PRRT) with radiolabeled SSAs in gastrinoma patients. The goal of one study was to assess the effect of PRRT on symptoms, gastrin secretion, and tumor load in patients with progressive malignant gastrinomas. It was retrospectively studied 11 patients with metastatic gastrinomas followed for a mean period of 6 years. All patients were symptomatically treated with PPIs, and 9 of 11 patients received monthly injections of SSAs; all patients had an Eastern Cooperative Oncology Group score of 0-1, and received PRRT (⁹⁰Yttrium- or ¹⁷⁷Lutetium-DOTATOC) for progressive disease. Serum gastrin measurements and radiological assessment (using the Response Evaluation Criteria in Solid Tumors criteria) were performed before and every 3-6 months following PRRT. PRRT induced symptomatic improvement in all patients. The mean serum gastrin decreased significantly from 4831 ml/L to 932.6 ml/L (normal, 40-108 ml/L). Periodic radiological surveillance showed complete response in 1 (9 %) patient, partial tumor response in 5/11 (45 %) patients, and tumor stabilization in 5/11 (45 %) patients. In 7/11 (64 %) patients, the antitumor effect of PRRT persisted after a median period of 14 months. Four of 11 (36 %) patients died due to tumor progression (median time to progression, 11 months); in this group, the mean survival time after the last PRRT was 14 ± 7 months [525].

Hyperinsulinemia

Profound hypoglycemia occurs rarely as a late complication after Roux-en-Y gastric bypass (RYGB). It was investigated the role of glucagon-like-peptide-1 (GLP-1) in four subjects who developed recurrent neuro-glycopenia 2 to 3 y after RYGB. A standardized test meal (STM) was administered to all four subjects. A 2 h hyperglycemic clamp with GLP-1 infusion during the second hour was performed in one subject, before, during a 4 wk trial of octreotide, and after 85% distal pancreatectomy. After cessation of both glucose and GLP-1 infusion at the end of the 2 h clamp, blood glucose levels were monitored for 30 min. Responses were compared with a control group (five subjects 12 mo status post-RYGB without hypoglycemic symptoms). During STM, both GLP-1 and insulin levels were elevated 3- to 4-fold in all subjects, and plasma glucose-dependent insulinotropic peptide (GIP) levels were elevated 2-fold. Insulin responses to hyperglycemia ± GLP-1 infusion in one subject were comparable to controls, but after cessation of glucose infusion, glucose levels fell to 40 mg/dL. During octreotide, the GLP-1 and insulin responses to STM were reduced (>50 %). During the clamp, insulin response to hyperglycemia alone was reduced, but remained unchanged during GLP-1. Glucagon levels during hyperglycemia alone were suppressed and further suppressed after the addition of GLP-1. With the substantial drop in glucose during the 30

min follow-up, glucagon levels failed to rise. Due to persistent symptoms, one subject underwent 85 percent distal pancreatectomy; postoperatively, the subject remained asymptomatic (blood glucose: 119-220 mg/dL), but a repeat STM showed persistence of elevated levels of GLP-1. Histologically enlarged islets, and beta-cell clusters scattered throughout the acinar parenchyma were seen, as well as β -cells present within pancreatic duct epithelium. An increase in pancreatic and duodenal homeobox-1 protein (PDX-1) expression was observed in the subject compared with control pancreatic tissue. It was concluded that a persistent exaggerated hypersecretion of GLP-1, which has been shown to be insulinotropic, insulinomimetic, and glucagonostatic, is the likely cause of post-RYGB hypoglycemia. The hypertrophy and ectopic location of β -cells is likely due to overexpression of the islet cell transcription factor, PDX-1, caused by prolonged hypersecretion of GLP-1 [526].

Insulinoma

Insulinoma is rare tumor with an incidence of approximately four cases per million per year. There are few large single-center series that focus on the surgical management strategy of insulinomas. Medical records of patients diagnosed as insulinoma from 1990 to 2010 were reviewed retrospectively. A total of 328 patients were diagnosed with insulinomas; 292 of them underwent 320 operations, which included 46 laparoscopic surgeries. Tumor enucleation was the most common operative procedure. Multiple tumors were found in 30 cases; 17 cases were multiple endocrine neoplasia-1 syndrome. Thirteen patients with malignant insulinomas underwent tumor resection. Pancreatic fistula (PF) was the most frequent complication, and the incidence of clinical PFs (Grades B and C) was 15 percent. There was no significant statistical difference between open and laparoscopic surgery in blood loss, operative time, and complications. Metachronous tumors were noted in 11 patients. It was concluded that surgery is the best treatment of choice for insulinoma patients. Surgical approach depends on tumor size, location, and its pathological characters. Laparoscopic management of insulinomas is feasible and safe for tumors located in the body or tail of the pancreas. Open surgery combined with intraoperative ultrasonography is recommended to avoid omission of lesions in patients with multiple insulinomas. An aggressive surgical approach is indicated for malignant insulinoma patients [527].

Congenital hyperinsulinism

Congenital hyperinsulinism (CHI) is a cause of persistent hypoglycemia. Histologically, there are two subgroups, diffuse and focal. Focal CHI is a consequence of two independent events, inheritance of a paternal mutation in ABCC8/KCNJ11 and paternal uniparental isodisomy of chromosome 11p15 within the embryonic pancreas, leading to an imbalance in the expression of imprinted genes. The probability of both events occurring within siblings is rare. It was described the first familial form of focal CHI in two siblings. The proband presented with medically unresponsive CHI. He underwent pancreatic venous sampling and Fluorine-18-L-dihydroxyphenylalanine positron emission tomography scan, which localized a 5-mm focal lesion in the isthmus of the pancreas. The sibling presented 8 year later also with medically unresponsive CHI. An Fluorine-18-L-dihydroxyphenylalanine positron emission-computerised tomography scan showed a 7-mm focal lesion in the posterior section of the head of the pancreas. Both siblings were found to be heterozygous for two paternally inherited ABCC8 mutations, A355T and R1494W. Surgical removal of the focal lesions in both siblings cured the Hyperinsulinaemic hypoglycaemia [528].

Paragangliomas

Paragangliomas are rare neuroendocrine neoplasms arising in extra-adrenal chromaffin cells of the autonomic nervous system. In rare instances, paragangliomas present around and involve the pancreas, thereby mimicking one of the more common primary pancreatic lesions. These neoplasms present considerable diagnostic difficulty not only for the clinician and radiologist but also for the pathologist. It was collected a series of 9 peripancreatic paragangliomas clinically simulating a primary pancreatic lesion. The paragangliomas were diagnosed in 4 men and 5 women with an age range of 37 to 78 years (mean, 50 years). Patients presented clinically either with diffuse epigastric and abdominal pain (7 of 9, 78 %) or with an incidental mass (2 of 9, 22 %) discovered on routine radiographic imaging. All patients were found to have mass lesions suspicious for a primary pancreatic neoplasm on radiographic examination. The lesions were predominantly located in the body of the pancreas (5 of 9, 56 %) and ranged in size from 6 to 17 cm (mean, 10.0 cm). Five of 9 (56 %) neoplasms also demonstrated cystic change. Fine-needle aspiration (FNA) was performed on 6 cases; however, the diagnostic accuracy was low, with 3 of 6 (50 %) neoplasms misdiagnosed as pancreatic neuroendocrine tumor (PanNET) (n=1), spindle cell neoplasm (n=1), or pseudocyst (n=1). In addition, 2 of 8 (25 %) surgically resected tumors were misdiagnosed by the referring pathologist as a PanNET. Immunohistochemistry was performed on all cases, confirming the characteristic 2-cell populations: chief cells (synaptophysin positive and chromogranin A positive) and sustentacular cells (S-100 protein positive). Follow-up information was available for all patients and ranged from 2 months to 12 years (mean, 3 years). Three of 9 (33 %) patients developed metastatic disease, and 2 of these 3 died of their disease at 3 and 5 years after diagnosis. In summary, in unsuspected cases, interpretation of FNA and surgical pathology resections can be diagnostically challenging. Awareness and proper recognition of this entity, including differential diagnosis, are imperative in establishing the correct diagnosis. Further, close follow-up of these cases should be considered because of the significant risk of metastatic disease [529].

Pancreatic duct tumors

Very few cases of primary neuroendocrine tumors of the main pancreatic duct have been reported. This paucity has hampered an accurate description of the distinctive clinical and pathological features of these tumors and the correct evaluation of the diagnostic and therapeutic problems which they may raise. It was reported five additional cases in order to underline the clinical, histological, and immunohistochemical features of this tumor entity. There were three male and two female, aged 43-72 years; in all patients, but one, who presented with epigastric pain, the diagnosis was made after the incidental discovery of a dilatation of the main pancreatic duct. The preoperative diagnosis was ductal adenocarcinoma in one case, IPMN in one case and neoplastic stenosis of unknown etiology in four cases. Surgical resection was performed in all cases. The diagnosis of neuroendocrine tumor was made at histological examination. All lesions were small, ranging from 5 to 15 mm. They had a predominantly intramural growth. The growth pattern was nodular in three cases, circumferential in two; there was no intra-luminal component. All cases were well-differentiated neuroendocrine neoplasms of low histological grade (G1); four cases expressed serotonin. One case was associated with regional lymph node metastases. All cases were cured by surgery alone; no recurrence was observed at the end of the follow-up period. In conclusion, despite their rarity, primary neuroendocrine tumors of the main pancreatic duct deserve recognition and must be considered in the etiological diagnosis of ductal stenosis [530].

Chromogranin A in ascites

Ascites secondary to neuroendocrine tumor metastases may arise from a variety of mechanisms. Our aim was to measure serum and ascitic chromogranin-A (CgA) to help determine whether ascites resulted from intraperitoneal/retroperitoneal disease burden or from other carcinoid complications such as congestive heart failure or portal hypertension. Patients with metastatic neuroendocrine tumors and ascites were identified. Chromogranin-A was obtained and measured from both serum and ascites. The causes of carcinoid ascites was categorized into two groups: high intraperitoneal or retroperitoneal disease burden (i.e. peritoneal metastases and/or lymphatic obstruction; n=12, group 1) or other organ-specific carcinoid complications such as CHF or portal hypertension (n=12, group 2). An ascites CgA/serum CgA ratio greater than 1 was more likely to be found in group 1. This ratio produced 100 percent sensitivity and 75 percent specificity for ascites secondary to peritoneal metastases and/or lymphatic obstruction. An ascites CgA/serum CgA ratio greater than 1 produces excellent accuracy in predicting peritoneal metastases and/or retroperitoneal disease as the cause of ascites in the setting of metastatic carcinoid. This test may play a role in the earlier identification of those patients who may be well served by aggressive management [531].

Microscopic periductal endocrine tumors of the pancreas

Intraductal papillary mucinous neoplasms constitute histologically distinctive pancreatic tumors characterized by cystically dilated pancreatic ducts lined by papillary epithelium, often with extensive mucin production. With increasing awareness of and vigilance for these tumors, there has been a surge in the incidence of intraductal papillary mucinous neoplasms in the last few decades. However, resections of presumed intraductal papillary mucinous neoplasms sometimes reveal other types of cystic lesions. Here we describe 3 cases of small, incidentally identified pancreatic endocrine tumors that focally compressed the main pancreatic duct and presented clinically, radiologically, and grossly as intraductal papillary mucinous neoplasm. The histology of the dilated ducts in all cases lacked convincing features of intraductal papillary mucinous neoplasm, prompting more careful examination of the specimens and eventual identification of small well-differentiated endocrine neoplasms. The constellation of findings represented by pancreatic endocrine neoplasm-associated duct stricture and dilatation can mimic intraductal papillary mucinous neoplasm clinically and pathologically. Awareness of this phenomenon can potentially avoid misdiagnosis of intraductal papillary mucinous neoplasm in such cases [532].

Cannabinoid receptors

The role of cannabinoid receptors in human islets of Langerhans has not been investigated in any detail, so the current study examined CB1 and CB2 receptor expression by human islets and the effects of pharmacological cannabinoid receptor agonists and antagonists on insulin secretion. Human islets were isolated from pancreases retrieved from heart-beating organ donors. Messenger RNAs encoding human CB1 and CB2 receptors were amplified from human islet RNA by RT-PCR and receptor localization within islets was identified by immunohistochemistry. Dynamic insulin secretion from human islets perfused with buffers supplemented with CB1 and CB2 receptor agonists and antagonists was quantified by radioimmunoassay. RT-PCR showed that both CB1 and CB2 receptors are expressed by human islets and immunohistochemistry indicated that receptor expression co-localized with insulin-expressing beta-cells. Perfusion experiments using isolated human islets showed that insulin secretion was reversibly stimulated by both CB1 and CB2 receptor agonists, with CB1 receptor activation associated with increased basal secretion whereas CB2 receptors

were coupled to initiation and potentiation of insulin secretion. Antagonists at CB1 (N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide) and CB2 (N-(1,3-Benzodioxol-5-ylmethyl)-1,2-dihydro-7-methoxy-2-oxo-8-(pentyloxy)-3-quinoline carboxamide) receptors failed to inhibit the stimulatory effects of the respective agonists and, unexpectedly, reversibly stimulated insulin secretion. These data confirm the expression of CB1 and CB2 receptors by human islets and indicate that both receptor subtypes are coupled to the stimulation of insulin secretion. They also implicate involvement of CB1/2 receptor-independent pathways in the antagonist-induced stimulatory effects [533].

Somatostatin

Sandostatin immediate release (IR) is frequently used to treat patients with carcinoid tumors. However, some patients are unable to tolerate the immediate side effects of sandostatin IR leading to discontinuation of the drug. There is no literature available to guide the management of patients' sensitivity/intolerance to sandostatin IR. It was reported a 49-year-old male with carcinoid tumor who was intolerant to sandostatin IR initially but was able to tolerate the drug after we employed a desensitization strategy [534].

Therapy overview

Constituting about 1-2 percent of all tumors of the pancreas, pancreatic neuroendocrine tumors (PNETs) are a subgroup of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) with distinct tumor genetics, biology, and clinicopathological features. Surgical resection is amenable only in a minority of the cases so systemic therapies are considered in most of them. The goals of medical treatment are to control the associated symptoms and signs of the specific tumors and to shrink the tumor mass. Somatostatin analogues can, not only decrease the secretion of peptides and inhibit their functions but also stop tumor growth. Other medical options for limiting tumor growth include interferon, systemic chemotherapy, and targeted therapies including, angiogenesis inhibitors, epidermal growth factor inhibitors, and mTOR inhibitors. Newer agents are tested and the treatment options expected to increase in the near future. Meanwhile optimal use of the available therapeutic strategies is critical [535].

PANCREATIC PSEUDOCYSTS

Endoscopic ultrasonography (EUS)-guided interventions have been used to treat patients with cystic lesions of the pancreas (CLPs). It was used EUS to guide injection and lavage of ethanol, followed by injection of paclitaxel, into cysts, and investigated treatment response and predictors. Fifty-two patients were enrolled in the study using the following inclusion criteria: unilocular or oligolocular cysts, indeterminate cystic lesions that required EUS fine-needle aspiration, and cystic lesions that grew during the observation period. Forty-seven patients were followed up for more than 12 months and their outcomes were analyzed. The mean diameter of the CLPs was 32 mm (range, 17-68 mm) and the estimated volume was 14 mL (range, 1-69 mL). Twenty CLPs were oligolocular. The mean level of carcinoembryonic antigen was 463 ng/mL (range, 1-8190 ng/mL). The median follow-up period was 22 months. A complete response was observed in 29 patients, a partial response in 6 patients, and persistent cysts in 12 patients. Four of 12 patients with persistent cysts underwent surgery. The histopathologic degree of epithelial ablation varied from 0 to 100 percent. Based on univariate analysis, EUS diameter and original volume predicted cyst resolution; in multivariate analysis, only original volume predicted resolution. Mild pancreatitis and splenic vein obliteration each occurred in 1 patient. EUS-guided injection and lavage of

ethanol, followed by injection of paclitaxel, appears to be a safe method for treating pancreatic cysts; 62 percent of patients had complete resolution. Small cyst volume predicted complete resolution [536].

Surgery is the treatment of choice for traumatic pseudocyst. Minimally invasive management of these collections has been used. The aim of one study was to analyze the outcome after endoscopic treatment and the integrity of the main pancreatic duct caused by abdominal trauma. A total of 51 patients with traumatic pseudocyst who underwent endoscopic therapy were studied. All were symptomatic with a persistent collection for more than 6 weeks. Endoscopic retrograde pancreatography allowed characterization according to Takishima classification (1, 2, and 3), in which guided therapy was divided into transpapillary drainage (Takishima 2 and 3 without bulging), transmural (type 1), or combined (type 2 or 3 with bulging). Endoscopic retrograde pancreatography was obtained in 47 (90 %) of 51 patients. Drainage was transmural in 13, combined in 24, and transpapillary in 10. The success and recurrence rates of endoscopic treatment were 94 percent and 8 percent, respectively. There were 9 complications but no procedure-related deaths. Patients with penetrating trauma had more recurrences and risk for development of infection than those with blunt trauma. It was concluded that endoscopic treatment of traumatic pancreatic collection is safe and effective and can be considered a first-choice alternative to surgical treatment. Endoscopic retrograde pancreatography and Takishima classification are useful in determining the best endoscopic approach [537].

PANCREATIC ANEURYSMS

The incidence of splenic artery aneurysms ranges from 0.1 to 10.4 percent in the general population, and it is 4 times more common in females than in males. Although the mechanism of pathogenesis is not fully understood, the risk factors include trauma, hormonal and local hemodynamic changes during pregnancy, portal hypertension, arterial degeneration, and atherosclerosis. Spontaneous rupture and hemorrhage is one of the most dangerous complications of this condition, with lifethreatening consequences. It was now reported multiple splenic artery aneurysms resulting in infarction of the spleen and regional portal hypertension. The clinical manifestation of splenic artery aneurysms is not specific, varying from lack of symptoms to excruciating upper or left upper quadrant abdominal pain after spontaneous rupture of aneurysms associated with hemodynamic failure. The natural course of splenic artery aneurysms is similar to other intra-abdominal aneurysms: gradual increases in size leading to eventual rupture. Although traditional surgical intervention has long been the mainstream of therapy, recent advances in imaging and minimally invasive techniques have revolutionized the diagnosis and management of splenic artery aneurysms, including laparoscopic surgery, endovascular embolization, and stent graft exclusion of the aneurysm. Conventional splenectomy is appropriate for patients with ruptured aneurysms and aneurysms with complications [538].

Pancreatic pseudocyst presented as pseudoaneurysm of the splenic artery is a potential serious complication in patients with chronic pancreatitis. A 42-year-old male patient with a long-standing evolution of chronic pancreatitis and 8-year long evolution of pancreas pseudocyst was referred due to worsening of the general condition. At admission, the patient was cachectic, febrile, and had the increased values of amylases in urine and sedimentation. After clinical and diagnostic examination: laboratory assessment, esophagogastroduodenoscopy (EGDS), ultrasonography (US), endoscopic ultrasonography (EUS), multislice computed scanner (MSCT) angiography, pseudoaneurysm was found caused by the conversion of pseudocyst on the basis of chronic pancreatitis. The patient was operated on after founding pancreatic pseudocyst, which caused erosion of the splenic artery and their

mutual communication. Postoperative course was duly preceded without complications with one year follow-up [539].

Inferior pancreatoduodenal artery

The authors reported a case of a 78-year old patient affected by multiple myeloma who develops acute pancreatitis and pseudoaneurysmal dilatation of the inferior pancreaticoduodenal artery causing erosion of the second portion of the duodenal wall and hematemesis. The authors focus first on the supposed etiological relationship between multiple myeloma and acute pancreatitis, and they assume that the therapeutic treatment for the bone marrow disease (bortezomib) may have triggered the pancreatic inflammatory response. They then analyze the pathogenesis of the vascular complication which seems to be related to the lytic action of pancreatic enzymes on the vessel wall which results in the formation of a pseudoaneurysm first and a pseudocyst then. The vascular complication was diagnosed by computed tomography (CT) thus avoiding selective angiography which was considered too invasive for the patient. The careful and conservative treatment of the complication has allowed for full healing of the cephalopancreatic region, in addition to avoiding surgery or embolization treatment of the pseudoaneurysm which is accompanied by a mortality rate as high as 50 [540].

NUTRITION IN PANCREATIC DISEASE

Nutritional status plays an important role in the incidence of postoperative complications and the prognosis of various tumours. The prognostic value of preoperative nutritional factors in patients with pancreatic cancer is not known. A retrospective study included 268 patients who underwent resection for adenocarcinoma of the pancreas. The predictive value of preoperative nutritional status for postoperative outcome (survival, complications) was assessed. Nutritional factors included the three constitutional indices, serum albumin and Onodera's prognostic nutrition index (PNI), calculated as $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$. In multivariable analysis preoperative low PNI (but not low albumin) was an independent prognostic factor for poor survival: hazard ratio (HR) 1.73. The accuracy of a PNI value of less than 45 as cut-off for clinically significant preoperative malnutrition in predicting 1- or 2-year survival after surgery was, however, limited (66 and 56 percent respectively). Low preoperative albumin concentration and PNI were significantly associated with postoperative complications: odds ratio 1.98 and 2.14, respectively. Low PNI and low body mass index were independently associated with pancreatic fistula: HR 2.52 and 0.40 respectively. It was concluded that the PNI is associated with overall survival and postoperative complications, in particular pancreatic fistula, in patients with pancreatic cancer. The moderate accuracy of PNI as a predictor of survival limits its clinical use [541].

An estimated 5 to 10 percent of patients with pancreatic cancer have an underlying germline disorder, whereas the remainder of cases is thought to result from damage to genes occurring during the life span of the individual. Smoking is a clear risk factor, implicated in 20 to 25 percent of pancreatic cancers. The interaction of diet and physical activity and the potentially associated diseases of obesity and diabetes are complex and can contribute to 30 percent of pancreatic cancers. However, most studies find little to no association between alcohol consumption and pancreatic cancer, except for the increased risk in patients with alcoholic chronic pancreatitis, but types 1 and 2 diabetes mellitus increase the risk of pancreatic cancer with a latency period of more than 5 years. The report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) "Food nutrition, physical activity and the prevention of cancer: a global perspective" summarizes the evidence base of reported associations between food, nutrition, physical activity, and

cancer of the pancreas. The expert panel determined that there is a probable association between foods containing folate and decreased risk of pancreatic cancer, whereas convincing evidence that higher body fatness, abdominal fatness, and adult attained height increase risk. Limited evidence suggests that fruit intake and physical activity decreases risk, whereas red meat intake increases risk. The primary guidance for federal nutrition policy and nutrition education activities is the Dietary Guidelines for Americans; the guideline 2010 was released on January 31, 2011. The DGA has been published jointly every 5 years since 1980 by the Departments of Health and Human Services and Agriculture, as required by federal legislation. The two overarching concepts of the recommendations 2010 are to maintain calorie balance over time to achieve and sustain a healthy weight and to focus on consuming nutrient-dense foods and beverages. The socioecological framework for nutrition and physical activity decisions is presented to remind us that multiple elements of society help shape an individual's food and physical activity choices and, ultimately, calorie balance and chronic disease risk. Both the guidelines 2005 and 2010 highlight the importance of fruits, vegetables, and whole grains in the diet. The relationships between these foods and cancer risk are also outlined in the WCRF/AICR report. However, active research programs in pancreatic cancer focus on the role of phytochemicals from plant foods on pancreatic carcinogenesis. Interesting results in preclinical studies show potential efficacy in inhibiting pancreatic carcinogenesis for a number of compounds, including curcumin, green tea polyphenols, genistein, isothiocyanates, and others. However, phytochemicals are thought not to be essential to the diet, so no daily requirement has been established for them. There are as many as 100,000 different phytochemicals, a large proportion of which are bioactive. Much more research is needed to fully assess the mechanisms of action, as well as the health-supporting properties of these compounds; only then can a public health recommendation around phytochemical intake be formulated. In the meantime, the DGA's emphasis on increasing not only the total quantity but also the variety of fruit and vegetables in the diet to provide a range of phytochemical and nutrient resources is well founded [542].

In pancreatitis

Nutritional support can have a significant beneficial impact on the course of moderate to severe acute pancreatitis. Enteral nutrition is preferred, with emphasis on establishment of jejunal access; however, parenteral nutrition can also be of value if intestinal failure is present. Early initiation of nutritional support is critical, with benefits decreasing rapidly if begun after 48 hours from admission. Severe malnutrition in chronic pancreatitis can be avoided or treated with dietary modifications or enteral nutrition [543].

In cancer

Nutritional support can have a significant beneficial impact on the course of moderate to severe acute pancreatitis. Enteral nutrition is preferred, with emphasis on establishment of jejunal access; however, parenteral nutrition can also be of value if intestinal failure is present. Early initiation of nutritional support is critical, with benefits decreasing rapidly if begun after 48 hours from admission. Severe malnutrition in chronic pancreatitis can be avoided or treated with dietary modifications or enteral nutrition. The components of Onodera's prognostic nutrition index (PNI) – serum albumin and total lymphocyte count – correlate with increased morbidity and mortality after a variety of types of surgery. Although inadequate nutrition in advanced pancreatic cancer may contribute to low serum albumin levels, given the marked acute-phase response present in this patient population and albumin's role as a negative acute-phase serum protein, the measurement cannot distinguish between albumin as a marker of nutritional status or aggressive cancer phenotype. The same is true of total lymphocyte count [544].

Pancreatic cancer is frequently associated with preoperative malnutrition. Pancreatic tumour cells express cytokines such as tumour necrosis factor alpha, which plays a key role in catabolic metabolism. Protein energy malnutrition causes physical change, typically resulting in weight loss. In addition, as an immunonutritional disorder, it causes a decline in albumin concentration, total lymphocyte count, helper T cells, interleukins 2 and 3, and T cellblastogenic responses. Nutritional status plays an important role in the incidence of postoperative complications and overall survival after resection of malignant tumours. Pancreatic cancer causes debilitating malnutrition and immunological deterioration with tumour growth. Additionally, gastrointestinal obstruction and biliary stricture resulting from tumour invasion can impair nutritional status. Aworsening nutritional status leads to increased susceptibility to infection, protracted wound healing, impaired blood clotting and vessel wall fragility, and directly increases the occurrence of postoperative complications. Moreover, it can contribute to tumour development through the suppression of tumour immunity. The concept of a prognostic nutrition index (PNI) was suggested by Smale and colleagues in 1981, and various PNIs have subsequently been considered for use as a clinical predictor for patients with cancer. Onodera's PNI is commonly employed in Japan, and was originally proposed as a preoperative risk factor and determinant of surgical indication in colorectal cancer. However, it is now used widely as a barometer of nutritional assessment not only in the field of gastrointestinal surgery but also by nutrition support teams for hospitalized patients. The prognostic value of preoperative nutritional factors in patients with pancreatic cancer is not known. Albumin is one of the most popular indicators of nutritional status, and has been correlated with postoperative complications. As the half-life of albumin is approximately 20 days, it reflects mid- and long-term nutritional status. Hypoalbuminaemia is associated with poor tissue healing, decreased collagen synthesis in surgical wounds or at anastomoses, and impairment of immune responses, such as macrophage activation and granuloma formation. One retrospective study included 268 patients who underwent resection for adenocarcinoma of the pancreas. The predictive value of preoperative nutritional status for postoperative outcome (survival, complications) was assessed. Nutritional factors included the three constitutional indices, serum albumin and Onodera's prognostic nutrition index (PNI), calculated as $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$. In multivariable analysis preoperative low PNI (but not low albumin) was an independent prognostic factor for poor survival: hazard ratio (HR) 1.73 (95 % confidence interval 1.21 to 2.47). The accuracy of a PNI value of less than 45 as cut-off for clinically significant preoperative malnutrition in predicting 1- or 2-year survival after surgery was, however, limited (66 and 56 %, respectively). Low preoperative albumin concentration and PNI were significantly associated with postoperative complications: odds ratio 1.98 (95 % confidence interval 1.18 to 3.32) and 2.14 (95 % confidence interval 1.23 to 3.73) respectively. Low PNI and low body mass index were independently associated with pancreatic fistula: HR 2.52 (1.37 to 4.63) and 0.40 (0.17 to 0.93) respectively. It was concluded that the PNI is associated with overall survival and postoperative complications, in particular pancreatic fistula, in patients with pancreatic cancer. The moderate accuracy of PNI as a predictor of survival limits its clinical use [545].

PANCREATIC TRAUMA

A rapid computed tomography technique or "trauma scan" (TS) provides high-resolution studies of the head, cervical spine, chest, abdomen, and pelvis. It was sought to determine whether TS has decreased missed injuries. A previous study of TS found a 3 percent missed rate. After institutional review board approval, trauma patients from 2001 through December were reviewed for delayed diagnosis (DD) of injury to the head, cervical spine, chest, abdomen, or pelvis. Missed extremity injuries were excluded. Injury Severity Score, length of stay, type of injury, outcomes, and days to detection were captured. Of 26,264 patients

reviewed, 90 patients had DD, with an incidence of 0.34 percent. DD most commonly presented on day 2. Injuries included 16 bowel/mesentery, 12 spine, 11 pelvic, 8 spleen, 6 diaphragm, 5 clavicle, 4 scapula, 4 cervical spine, 4 intracranial, 4 sternum, 3 maxillofacial, 3 liver, 2 heart/aorta, 2 vascular, 2 urethra/bladder, 2 pneumothorax, and 2 pancreas/common bile duct. DD resulted in 1 death, 6 prolonged intensive care unit stays, 19 operative interventions, and 38 additional interventions. It was concluded that TS is an effective way of evaluating trauma patients for intracranial, cervical spine, chest, abdomen, and pelvic injuries that have the potential to impact morbidity and mortality. The incidence of injuries missed in these crucial areas has been reduced at our institution by the use of this radiographic modality. The most common missed injury remains bowel, and so a high index of suspicion and the tertiary survey must remain a mainstay of therapy [546].

Injuries to the pancreas are uncommon, but may result in considerable morbidity and mortality. One study evaluated the management of blunt pancreatic injuries using a previously defined protocol to determine which factors predicted morbidity and mortality in all adult patients with blunt pancreatic injuries treated at a level 1 trauma centre between 1981 and 2009. One hundred and ten patients (92 men, 18 women; mean age 30 years, range 13-68 years) were treated during the study period. Forty-six patients had American Association for the Surgery of Trauma (AAST) grade 1 or 2 pancreatic injuries and 64 had AAST grade 3, 4 or 5 pancreatic injuries. Injuries involved the head (n=21), neck (n=15), body (n=48) and tail (n=26) of the pancreas. The mean number of organs injured was 2.7 per patient (range 1-4). One hundred and one patients underwent a total of 123 operations, including drainage of the pancreatic injury (n=73), distal pancreatectomy (n=39) and Whipple resection (n=5). The overall complication rate was 75 percent and the mortality rate 16 percent. Only 2 of the 18 deaths were attributable to the pancreatic injury. Shock on presentation was highly predictive of death; 17 of 39 patients with shock died, compared with 1 of 71 patients who were not shocked. Fourteen of 46 patients with grade 1 and 2 pancreatic injuries died compared with 4 of 64 patients with grades 3, 4 and 5 injuries. Mortality increased exponentially as the number of associated injuries increased. Two of 57 patients with injury to the pancreas only or one associated injury died, compared with 16 of 53 with two or more associated injuries. The study thus demonstrated a significant correlation between the AAST grade of injury and pancreas-specific morbidity and between shock on admission, the number of associated injuries and death, in patients with blunt pancreatic injuries. Although morbidity and mortality rates after blunt pancreatic trauma are high, death was usually the result of major associated injuries and not related to the pancreatic injury [547].

The justification for pancreatoduodenectomy (PD) for extended duodenal and pancreatic caustic necrosis is still a matter of debate. This was a retrospective evaluation of patients who underwent PD in association with oesophagogastrrectomy from a large single-centre cohort of patients with caustic injuries. Morbidity, mortality and long-term outcome were assessed. PD was performed in 18 (7 percent) of 273 patients who underwent emergency surgery for caustic injuries. Biliary and pancreatic duct reconstruction during PD was performed in ten and six patients respectively. Seven patients died and 17 experienced operative complications after PD for caustic injuries. Twelve patients required at least one reoperation. Specific PD-related complications occurred in 13 patients. Initial or secondary extension of necrosis to adjacent organs were independent predictors of operative death. After a median follow-up of 24 months following reconstruction, three patients had recovered nutritional autonomy. In an intention-to-treat analysis, functional success was recorded in three patients and the 5-year survival rate was 39 per cent after PD for caustic injury. It was concluded that pancreatoduodenectomy can save the lives of patients with caustic injuries extending beyond the pylorus, but has poor functional outcome. Immediate pancreatic duct reconstruction should be preferred to duct occlusion to decrease the rate of pancreatic complications [548].

Epidemiology

Walking is the primary mode of transportation for people aged 65 year and over; hence pedestrian injuries are a substantial source of morbidity and mortality among elderly patients in the United States. One study was aimed at evaluating the pattern of injury in the elderly pedestrians and how it differs from younger patients. Retrospective analysis of the National Trauma Data Bank (2002-2006) was performed, with inclusion criteria defined as pedestrian injuries based on ICD-9 codes, excluding age < 15 years. The following age categories in years were created: 15-24 (reference group), 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85-89. The injury prevalence was compared, and multivariate regression for mortality was conducted adjusting for demographic and injury characteristics. A total of 79,307 patients were analyzed. Superficial injuries were the most common at 29 percent, with lower extremity fractures and intracranial injuries following at 25 percent and 21 percent respectively. The very elderly (75-84 and 85-89) had significantly higher rates of fractures of the pelvis (16 % and 17 % vs 8 % in the youngest group), upper (19 % and 18 % vs 9.8%), lower extremities (31 % and 32 % versus 23 %) and intracranial injuries (26 % and 29 % versus 22 %), but sustained lower rates of hepatic (2 % and 2 % vs 3 %) injuries, with no difference seen in pancreatic, splenic, and genitourinary injuries. On multivariate analysis, very elderly patients were six to eight times more likely to die [549].

Damage control laparotomy

Damage control laparotomy (DCL) has beneficial effects on the long-term morbidity and survival of trauma patients. Eighty-eight trauma patients who were admitted during a 3-year period (2000 through 2003) underwent damage control laparotomy and were subsequently followed up (2001 through 2008). On admission, the mean age and Injury Severity Score were 33 years and 34, respectively. Of the 88 patients, 66 (75 %) were male; 46 patients had blunt injuries and 42 had penetrating injuries. Liver was the most common injury (63 patients), followed by bowel (34), spleen (33), major vessel (19), and pancreas (10). The mean admission pH and temperature were 7.19 and 34.4°C, respectively, with 21.5 U of packed red blood cells transfused. The mean (SD) number of initial abdominal operations was 4.6 (2.5) per patient, with an overall mortality of 28 percent (25 patients). Intensive care unit and hospital lengths of stay were 18 (15) and 32 (20) days, respectively. Of the 63 patients who survived, 58 underwent intra-abdominal closure with polyglactin mesh. During the study, 44 intra-abdominal infections and 18 enterocutaneous fistulas were diagnosed. All 63 survivors were readmitted at least once. There were a total of 186 readmissions and 92 subsequent surgical procedures. Ventral hernia repair (66 readmissions) was the most common reason for readmission, followed by infection (41) and fistula management (29). There was 0 percent mortality for patients who survived the preliminary hospitalization. Of the 63 surviving patients, 51 (81 %) reported that they had gone back to work and resumed normal daily activities. It was concluded that although damage control laparotomy is associated with a significant complication and readmission rate, its overall benefit is indisputable [550].

PANCREATIC INFECTIONS

Hepatitis E

Hepatitis E is a form of acute hepatitis, which is caused by infection with hepatitis E virus. The infection is transmitted primarily through fecal-oral route and the disease is highly endemic in several developing countries with opportunities for contamination of drinking water. In these areas with high endemicity, it occurs as outbreaks and as sporadic cases of acute hepatitis. The illness often resembles that associated with other hepatotropic viruses and is usually self-limiting; in some cases, the disease progresses to acute liver failure. The

infection is particularly severe in pregnant women. Patients with chronic liver disease and superimposed HEV infection can present with severe liver injury, the so-called acute-on-chronic liver failure. In recent years, occasional sporadic cases with locally acquired hepatitis E have been reported from several developed countries in Europe, United States, and Asia. In these areas, in addition to acute hepatitis similar to that seen in highly endemic areas, chronic hepatitis E has been reported among immunosuppressed persons, in particular solid organ transplant recipients. HEV-infected mothers can transmit the infection to foetus, leading to premature birth, increased fetal loss and hypoglycaemia, hypothermia, and anicteric or icteric acute hepatitis in the newborns. Occasional cases with atypical non-hepatic manifestations, such as acute pancreatitis, hematological abnormalities, autoimmune phenomena, and neurological syndromes have been reported from both hyperendemic and non-endemic regions. The pathogenesis of these manifestations remains unclear [551].

Hepatitis E is an emerging imported disease in Europa but autochthonous cases are described for some years. Extra-hepatic associated manifestations are published. It was reported a case of acute necrotizing pancreatitis associated with imported acute viral E hepatitis (genotype 1a) in a 26 years old French man travelling and originated from Pakistan. The outcome is favourable spontaneously in two months. This life-threatening hepatitis E related complication is unknown in Europa where genotype 3 virus strains prevail. The clinical presentation is stereotyped with the onset of pancreatitis in the second or third weeks of hepatitis evolution in an Indian male in his second or third decade infected with genotype 1 strain. No pancreatitis-related death is reported in the 13 previous reported cases [552].

Actinomycosis

It was reported a case of purulent actinomycosis and incidental T1-carcinoid of the pancreatic head [553].

CMV

It was reported a successfully treated pancreatitis caused by a CMV infection in a lupus patient [554].

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