RANDOMIZED TRIALS IN EXOCRINE PANCREATIC CANCER

Åke Andrén-Sandberg, Mats Hedberg & John Neoptolemos

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

AUTHORS' PREFACE

In the medical scientific hierarchy, *meta-analyses* based on many randomized studies (of good quality!) have the highest rank and their results are discussed as *evidence based medicine.* Second to the meta-analyses are *randomized controlled trials, RTCs.* At the very bottom of the same scale there are "personal communication (eminence based medicine)", case reports and abstracts from meetings. The lower one goes in the hierarchical list, the more papers it is possible to find. However, also the RTCs are after a while numerous, and it may be difficult to remember what has been done and what was the results or the investigations. Meta-analyses may compile the RTCs nicely, but sometimes not all are included, and sometimes a reader want sto know more of what is behind the meta-analyses. Therefore we have collected all the RTCs there are – with the seletion criteria given below – in our limited clinical and research area.

This means that randomized controlled trials, RTCs, are not all – there may as well be technically lousy RTCs, RTCs with clinically not relevant questions, and RTCs whose results are poorly discussed – but in general the RTCs are good steps on the way to know *what* we know and what we *don't know.*

We have collected all the RTCs we could easily find on pancreatic cancer and filed each RTC under some heading that can make a clinical difference. This collection can then hopefully be used:

- to get an overview of what questions that has been looked in pancreatic cancer management
- to get an overview of the evolution of RTCs
- to get a view of medical history concerning part of pancreatology
- to form a registry where it may be easy to find relevant articles when needed to treat individual patients, but also to plan research, give lectures etc
- to improve upcoming research, i.e. not to repeat old research misstake again – if research mistakes should be done: make new!
- from an academic point of view to define what we know and what we don't know on pancreatic cancer

According to the Cochran language evidence-based medicine (and surgery!) is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services. Sackett and coworkers stated "the practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research". Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors. Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits that patient best. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. To help identify which forms of health care work, which do not, and which are even harmful, results from similar trials need to be brought together. Trials need to be assessed and those that are of good quality and unbiased can be combined to produce both a more statistically reliable result and one that can be more easily applied in other settings. This combination of trials needs to be done in as reliable a way as possible. It needs to be systematic. A systematic review does not need to contain a statistical synthesis of the results from the included studies. If the results of the individual studies are combined to produce an overall statistic, this is usually

called a meta-analysis. A meta-analysis can also be done without a systematic review, simply by combining the results from more than one trial.

The scientific literature also in small medical subjects like pancreatology is today enormous – and it is not possible to keep updated unless making very strong and focused efforts. The present review is an attempt to make it easier for clinical pancreatologists to keep updated. From the beginning the review was an effort to make the reviewers updated, but hopefully it can be used also of others with the same interest, i.e. clinical pancreatology. However, it will still be a personal review, which means that the selection of presented articles has been those found by the reviewers, and other authors might have found more or less. We have used PubMed systematically with the MeSH "pancreatic cancer" and "randomized controlled trials", and from reading those articles we have found a few more. We have also selected some meta-analysis where appropriate; but there are not seldomly many on the same subject, and then only one is chosen, except if the meta-analyses have reached obvious different conclusions. Despite our efforts, it is not unprobable that there still are some articles that have been hidden under other heading – if you know where we can find those, please let us know (maybe there will be a new edition later on).

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Åke Andrén-Sandberg   Mats Hedberg   JohnNeoptolemos

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SELECTION CRITERIA

The authors of this book have made it very easy for themselves concerning selection of studies: found in PubMed under the MeSH "pancreatic cancer AND randomized trials" and available there at latest December 31, 2009. Those found this way have been read in total – some with a little help from Italian, Spanish, Japanese and Chinese colleges – and after that those remain that:

- investigate a clinical problem in patients with *exocrine* pancreatic cancer (no animal studies, no other periampullary tumors)
- randomized (blinding for the investigators) the subjects into at least two groups
- only full papers with abstracts available (if only abstracts available the study was omitted)
- declare in an understandable way how the study was performed and how the results were handled (statistics)
- published in a journal that was made available at the University Library at Karolinska Hospital, Stockholm

As the studies selected cover many years and comes from both priviliged and not-priviliged countries the quality differs even between the randomized studies. This has, however, not been taken into account in this book – the reader who is in doubt of the quality of a study cited has to go by the reference list to the paper and find out the quality of the original article him- or herselves. We have not been and do not intend to judges of study quality this time.

Also, there are some problems with probably duplication of results in prolonged randomized studies (?), but also meta-analyses that have been performed with some year's intermission with the same authors. We have in each case tried to only include the last publication, but if there have been doubts if it is the same materials both have been included.

Of special interest is it to find meta-analyses of the same or almost the same randomized trials but with different conclusions. We have then left to the readers to be the judges!

There are given *summaries* when there are many randomized trials found in the same field and in some instances *comment* on a certain study. These summaries and commentaries are the authors interpretation of the results of the single or combined randomized trials put in the study(s) clinical perspective. This means that after reading the articles thoroughly, the authors of this book have attempted to draw conclusions based on both fact and own experience – i.e. "eminence based medicine". The authors are happy to discuss these conclusions with those who have other opinions on how to do these interpretations.

It is the author's intention (and hope) that this book should be printed in at least a second edition – together with randomized trials present in PubMed also after December 31, 2009. If we have missed randomized trials up to this point for some reason we are happy to include them in the next edition, as long as they fulfill the criteria above (which also means that it is not enough with an abstract, but it is needed a full paper that could be evaluated properly).

And … we are happy to recieve responses from the users of this book: critical *and* non-critical, because that is the only way to make the next edition better.

Reporting results

In the book there is less emphasis on the oldest reported studies, which *might* have been good, but certainly in some instances used medical and scientific medthods that is obsolete

today – and usually has a lesser standard with regard both to the quality of the technique and the reporting. In each group therefore the oldest reports are at the bottom, and the newer are higher up, and is usually given more space.

However, it must be emphasized – once again – that this book should be seen only as an introduction to these randomized studies, and all of them have merits of their own that make them worth to read. Most of the text is just copies of abstracts (or rather "abstracts of abstracts"), with no intention to go deeper in the full paper – even though each has been read through at least of one of the authors of this book. The book aims at giving an overview of what has been done in the different fields, with the hope that the studies to come should not be simple repetitions of what has already been done, but using the knowledge gained – in pancreatology and in scientific progress – to perform even better studies in the future, and to solve new, important questions. There are still more questions than answers out there, so take this compliation as a start to make your own contribution.

There must be made some limitations, otherwise a review in this form should not be possible to write due to lack of time and lack of brain capacity, and probably not possible to read either. Regarding the limitations, first of all almost all of the articles have been read in their full length, but the writing here is based on their abstracts for practical reasons. This is also in line with the aim of the review: not to report all what has been published, but rather to give an introductional sample that hopefully will make the reader eager to read the whole article or articles: "a tast of randomized trials on pancreatic cancer up to 2010".

Another limitation is that almost all articles dealing with purely transplantation and diabetes (and most of endocrine pankreas) issues have been dropped.

The numbering of references might also need a comment. The references are numbered from 001, 002, 003 and onwards. This is because this kind of book of course first of all should be used through the computer and internet. As most ordinary pancreatologists use Microsoft's "Word" the readers are familiar with their *search* mode. So if you look for the reference 005 it is easy to find it both ways, but if you look for reference 5 it is impossible. Therefore all these zeros are present in the first part of the reference list.

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

LIST OF ABBREVIATIONS

AA	arachidonic acid
9AC	9-aminocamptothecin
ADCC	antibody-dependent cellular cytotoxicity
ADM	adriamycin
AMF	5-fluorouracil, doxorubicin, and mitomycin C
Ara-C	cytosine arabinoside
ATBC	alpha-tocopherol beta-carotene cancer prevention study
AZQ	aziridinylbenzoquinone
BPI	brief pain inventory
CAC	cisplatin, cytosine arabinoside, and caffeine
CAI	celiac axis infusion
CAP	capcitabine
CapGem	capecitabine plus gemcitabine
CapOx	capecitabine plus oxaliplatin
CBR	clinical benefit response
CCK	cholecystokinin
CEA	carcinoembryonic antigen
CI	confidence interval
CML	chronic myeloic leukemia
CR	complete response
CRT	chemoradiotherapy
CRT	conformal radiotherapy
CSF	cerebrospinal fluid
CT	computed tomography
DDP	cisplatin
DFS	disease-free survival (time)
DGE	delayed gastric emptying
DHAD	dihydroxyanthracenedione
DHR	delayed hypersensitivity response
DP	distal pancreatectomy
EBRT	external-beam radiotherapy
EGFR	epidermal growth factor receptor type 1
DHA	docosahexaenoic acid
DPH	delayed postoperative hemorrhage
DVT	deep venous thrombosis
ECOG	Eastern cooperative oncology group
EEN	early enteral nutrition
EMBE	expandable metallic biliary endoprothesis
EMS	expandable metal stents
EN	enteral nutrition
EPA	eicosapentaenoic acid
EPD	extended pancreaticoduodenectomy
ERCP	endoscopic retrograde cholangiopancreatography
ES	endoscopic sphincterotomy
ESPAC	European study group for pancreatic cancer
EUS	endoscopic ultrasonography
FA	folinic acid
FAACT	functional assessment of anorexia/cachexia therapy
FACIT-F	functional assessment of chronic illness therapy-fatigue
FACT	functional assessment of cancer therapy
FACT-Hep	functional assessment of cancer therapy-hepatobiliary
FAM	5-fluorouracil, doxorubicin, and mitomycin C

FAM-S	5-fluorouracil, doxorubicin, mitomycin C, and streptozotocin
FDR	fixed dose rate
FELv	5-fluorouracil, leucovorin, and etoposide
FEM	5-fluorouracil, epirubicin, and mitomycin C
FLEC	5-fluorouracil, leucovorin, epirubicin, and carboplatin
FLP	5-fluorouracil, folinic acid or leucovorin and cisplatin
FNCLCC	French Federation of Cancer Centers
FP	5-fluorouracil and cisplatin
FSM	5-fluorouracil, streptozotocin, and mitomycin C
5-FU	5-fluorouracil
FUP	5-fluorouracil and cisplatin
Gem	gemcitabine
GEM-CAP	gemcitabine and capecitabine
GemOx	gemcitabine and oxaliplatin
GERCOR	French multidisciplinary clinical research group
GH	growth hormone
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GITSG	Gastrointestinal tumor study group
Gln	glutamine
GOIRC	Italian oncology group for clinical research
GU	gemcitabine and uracil/tegafur
HAP	hypoxic abdominal perfusion
HCPS	hydromer-coated polyurethane stents
HER1	human epidermal growth factor receptor type 1
HR	hazard ratio
HYC	hycanthone
IEF	immune-enhancing formula
IFN	interferon
IFO	ifosfamide
Ig	immunoglobulin
INCa	French National Cancer Institute
IOR/IORT	intraoperative radiotherapy
KPS	Karnofsky performance score
KW	Kausch-Whipple (type of pancreatic resection)
LAB	lactobacillus
LBM	lean body mass
LH-RH	luteinizing hormone-releasing hormone
LiGLA	lithium gamolenate
LMWH	low molecular weight heparin
LOS	length of hospital stay
LV	leucovorin
mFOLFIRI.3	modified FOLFIRI.3 (5-FU, folinic acid, and irinotecan)
mFOLFOX	modified FOLFOX (folinic acid, 5-FU, and oxaliplatin)
MGBG	methylglyoxal-bis-guanylhydrazone
MMC	mitomycin-C
MRCP	magnetic resonance cholangiopancreatography
MSCT	multislice CT
MTD	maximum tolerated dose
9NC	9-Nitrocamptothecin
NCPB	neurolytic coeliac plexus blockade
NK	natural-killer (cells)
NNT	needed to treat
ORR	overall response rate
OS	overall survival

OXA	oxaliplatin
OXFU	oxaliplatin and infusional 5-FU
PALA	N-(phosphonacetyl)-L-aspartic acid
PCS	port catheter system
PD	pancreatoduodenectomy
PDGFR	platelet-derived growth factor receptors
PE	polyethylene
PE	pulmonary embolism
PEFG	cisplatin, epirubicin, 5-fluorouracil, and gemcitabine
PF	pancreatic fistula
PFS	progression-free survival
PG	pancreatogastrostomy
PJ	pancreatojejunostomy
PN	parenteral nutrition
POD	postoperative day
POPF	postoperative pancreatic fistula
PP	pylorus-preserving
PPPD	pylorus-preserving pancreatoduodenectomy
PPPD-PG	pylorus-preserving pancreaticoduodenectomy with gastric partition
PPPD-PJ	pylorus-preserving pancreaticoduodenectomy with pancreaticojejunostomy
PR	partial response
PRO	patient-reported outcomes
PS	performance status scale
PSS	patient satisfaction scale
PVI	protracted venous infusion
QOL	Quality of life
RBP	retinol binding protein
RECIST	response evaluation criteria in solid tumours
RFA	radiofrequency ablation
RIAC	regional intra-arterial infusion chemotherapy
r-HuEPO	recombinant human erythropoietin
RR	response rate
RT	radiotherapy
SEMS	self-expanding metal stents
SF-36	Short-Form 36 general health survey
SMF	streptozotocin, mitomycin, and 5-fluorouracil
SNB	splanchnic nerves neurolytic blockade
SW	standard whipple
SWOG	Southwest oncology group
SWPD	standard Whipple pancreaticoduodenectomy
TEN	total enteral nutrition
TNCD	National Thesaurus of Gastrointestinal Cancer
TNF	tumour necrosis factor
TP	true positive
TPN	total parenteral nutrition
TS	thymidylate synthase
TTP	time to tumor progression
UFT	uracil/tegafur
US	ultrasonography
VAS	visual analogue scale
VTE	venous thromboembolic events
QOL	quality of life

PHYSIOLOGY

Postoperative regeneration

Although pancreatic regeneration after resection is well documented in animals, atrophy rather than regeneration of the distal remnant pancreas commonly occurs following pancreatoduodenectomy in humans. Of the many factors involving pancreatic regeneration, gastrin has been shown to have trophic effect on the pancreas in an animal model. To investigate whether gastrin has regenerative effect on the pancreas and in particular whether it prevents the atrophy of the distal pancreas after resection of pancreas in humans. Between 1999 and May, a randomized prospective study was performed in 56 patients who underwent pylorus-preserving pancreatoduodenectomy for periampullary neoplasms. Patients were allocated to either a lansoprazole group or a control group. The lansoprazole members were given oral lansoprazole (30 mg/d) over 12 weeks postoperatively to induce hypergastrinemia. During the study period, 19 patients were excluded for different reasons; in the end a total of 37 patients (lansoprazole, n=18; control, n=19) were eligible for study. The volume of the distal pancreas as determined using thin-sectioned spiral CT data, nutritional status, and endocrine (insulin level, glucose tolerance test) and exocrine function (stool elastase) of the pancreas and serum gastrin levels were measured before surgery and 3 months after surgery. The two groups were clinically comparable. Serum gastrin level was elevated in the lansoprazole group. In this group, the mean volume of the distal pancreas was reduced by 10 percent after pylorus-preserving pancreatoduodenectomy, whereas severe pancreatic atrophy occurred in the control group. Postoperative insulin and stool elastase levels were higher in the lansoprazole group than in the control group. This study is the first prospective randomized trial of induced hypergastrinemia on the regeneration of the pancreas in humans. It may be possible to use induced hypergastrinemia in the treatment or prevention of pancreatic insufficiency following resection or injury [001].

DIAGNOSTICS

Endoscopic ultrasonography (EUS)

Clinical value of endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is today in many places an integrated part of the pretherapeutic evaluation program for patients with upper gastrointestinal (GI) tract cancer. Whether the clinical impact of EUS differs between surgeons from different countries is unknown. The same applies to the potential clinical influence of EUS misinterpretations. The aim of one study was to evaluate the interobserver agreement on predefined treatment strategies between surgeons from four different countries, with and without EUS, and to evaluate the clinical consequences of EUS misinterpretations. One hundred patients with upper GI tract cancer (including pancreatic cancer) were randomly selected from all upper GI tract cancer patients treated in a Danish University Hospital between 1997 and 2000. Based on patient records and EUS database results, a case story was created with and without the EUS result for each patient. Four surgeons were asked to select the relevant treatment strategy in each case, at first without knowledge of the EUS and thereafter with the EUS result available. Interobserver agreement and impact of EUS misinterpretations were evaluated using the actual final treatment of each patient as reference. Three of four or all four surgeons agreed on the same treatment strategy for nearly 60 percent of the patients with and without the EUS results. Treatment decisions were changed in 34 percent based on the EUS results, and the majority of these changes were toward nonsurgical and palliative treatments (85 %). Interobserver agreement was relatively low, but overall EUS increased kappa values from 0.16 ("poor") to 0.33 ("fair"), thus indicating increased overall agreement after the EUS results were available. EUS conclusion regarding stage or resectability was wrong in 17 percent of the cases, but only one serious event would have been the clinical result of EUS misinterpretations [002].

> Comment: This kind of studies is importand as it is easier to start with new modalities in the clinic than to get rid of older ones. It must be underlined that the study confirmed that the strongest clinical possibilities of EUS so far is its the ability to detect nonresectable cases.

Linear array or radial scanning?

A prospective comparison was undertaken to assess the accuracy of linear array and radial scanning EUS for staging pancreatic cancer. Patients with pancreatic cancer referred for EUS staging were randomized to linear array or radial scanning EUS. Staging accuracy for each was determined by comparison to surgical pathology in those patients going to surgery. Seventy-nine patients with pancreatic cancer were enrolled and 33 had surgical resection. Of these, 17 patients were randomized to linear array and 16 to radial scanning EUS. The remaining 46 patients did not have surgery because of comorbid illness or clinically unresectable disease. EUS staging accuracy for linear array was 94 percent (16 of 17) for T and 71 percent (12 of 17) for N staging, whereas radial scanning was 88 percent (14 of 16) for T and 75 percent (12 of 16) for N staging. For predicting vascular invasion, radial scanning was 100 percent accurate (16 of 16) while linear array was 94 percent (16 of 17) accurate. There was one false-negative assessment of invasion using linear array EUS. The authors concluded that overall, both EUS designs appear equivalent for staging pancreatic cancer and assessing vascular invasion [003].

EUS-guided fine needle aspiration cytology

Diagnosing pancreatic cancer by EUS-FNA is a potentially appealing alternative to percutaneous biopsy. In a single center, prospective, randomized, cross-over study it was compared EUS-FNA with CT- or US-guided FNA for diagnosing pancreatic cancer. Eighty-four patients referred with suspicious solid pancreatic mass lesions randomized to CT/US-FNA (n=43) or EUS-FNA (n=41). If cytology was nondiagnostic, cross over to the other modality was offered. Final outcome was determined by clinical follow-up every 6 months for 2 years and/or surgical pathology for patients with negative FNA. There were 16 true positive (TP) by CT/US-FNA and 21 TP by EUS-FNA. Sixteen of the 20 CT/US-FNA negative patients crossed over to EUS-FNA; 12 underwent FNA, 4 had no mass at EUS. Seven of the 12 had positive EUS-FNA. Eight EUS-FNA negative crossed over to CT/US; 4 had no mass at CT/US, 3 remained true negative throughout follow-up, 1 had chronic pancreatitis at surgery. The sensitivity of CT/US-FNA and EUS-FNA for detecting malignancy was 62 percent and 84 percent, respectively. However, a comparison of the accuracy for CT/US-FNA and EUS-FNA was not statistically significant. I should be mentioned that failure to meet target enrollment resulted in an inability to demonstrate a statistically significant difference between the two modalities. This means that EUS-FNA is numerically (though not quite statistically) superior to CT/US-FNA for the diagnosis of pancreatic malignancy [004].

> *Comment: As ultrasonography-based biopsy is cheaper than CT-guided biopsy some kind of ultrasonography-based biopsy should be preferred; possibly EUS-based if this is available.*

Instrumental aspects

The aim of one prospectively randomized study was to compare two commercially available needle assemblies with regard to handling and cytopathological yield. A total of 30 patients (19 men, 11 women; mean age 61) with focal pancreatic lesions underwent EUS-FNA with each of the two needles (GIP, Wilson-Cook). The sequence was randomized for the examiner and blinded for the cytologist. Three patients had to be excluded because of the impossibility of sample assignment or patient follow-up. EUS-FNA was performed using the standard technique with linear echo endoscopes. None of the characteristics evaluated by the examiner differed significantly between either of the needles. Inadequate results were obtained in 11 percent using the GIP needle, but in none with the Wilson-Cook needle. GIP needle cytology revealed malignancy in 11 patients (sensitivity, specificity, and accuracy were 55 %, 100 %, and 65 %, respectively, including inadequate results). The aspirates obtained with the Wilson-Cook needle identified malignancy in 16 patients (sensitivity, specificity, and accuracy were 85 %, 100 %, and 89 %, respectively). This means that there were no statistically significant differences were detected in the handling of either of the two needle assemblies. Nevertheless, cytopathologic results were significantly better with the Wilson-Cook needle [005].

A new mechanical puncture-echoendoscope was evaluated by comparing it with conventional linear and radial echoendoscopes. The new instrument has a 300 degrees image field parallel to the axis of the echoendoscope, which could potentially improve accuracy and facilitate assessment of suspected pancreatic lesions before needle puncture. Twenty consecutive patients with suspected pancreatic lesions were evaluated endosonographically, including fine needle aspiration (FNA). The initial assessment was performed by random selection of either the new instrument or the standard linear echoendoscope. After completing the assessment including FNA, the procedure with FNA was repeated with the other puncture echoendoscope. The findings with these 2 instruments were compared to those with the conventional radial scanning echoendoscope. FNA was performed in 17 patients with pancreatic head lesions. In 3 patients without a visible

pancreatic mass lymph, nodes greater than 10 mm in diameter were aspirated. The ability to image the needle, number of punctures, and material obtained were comparable for both puncture echoendoscopes. There were no significant differences with regard to time required for FNA with both puncture echoendoscopes or in the assessment of surrounding structures with all 3 instruments. The results of cytopathologic evaluation of material obtained by FNA were similar in 15 cases. The new instrument could not be passed into the esophagus in 1 patient because of an esophageal stricture. This means that the performance of the new mechanical puncture echoendoscope was satisfactory for assessment and FNA of pancreatic lesions. The additional use of the conventional radial scanning echoendoscope provided no advantage with regard to any parameter assessed [006].

Computed tomography (CT)

Individualized scan

In a study it was prospectively assess whether high contrast material flow rate (8 mL/sec) and individualized scan delay improve enhancement of normal pancreas with multidetector computed tomography (CT) and, as a result, tumor-to-pancreas contrast of pancreatic adenocarcinoma. Forty patients were recruited (21 women, 19 men; mean age, 67 years). Patients were referred for multidetector CT because they were suspected of having a pancreatic tumor and were randomized to receive 150 mL of nonionic contrast material (300 mg of iodine per milliliter) at a flow rate of 4 mL/sec (n=21) or 8 mL/sec (n=19). Patients underwent dynamic scanning at one level every 2 seconds for 66 seconds after intravenous administration of contrast material. Contrast enhancement of pancreas and tumors was measured with circular regions of interest. Peak contrast enhancement in pancreas was observed significantly earlier (mean +/- standard deviation) 29 seconds $\pm$ 4 versus 48 seconds $\pm$ 5) and was significantly higher (129 HU $\pm$ 26 vs 106 HU $\pm$ 35) with a flow rate of 8 mL/sec than with a flow rate of 4 mL/sec. Tumor-to-pancreas contrast greater than 40 HU lasted significantly longer with a flow rate of 8 mL/sec than with a flow rate of 4 mL/sec (26 seconds $\pm$ 12 versus 9 seconds + 8). With a flow rate of 8 mL/sec, an individualized scan delay of 19 seconds after aortic transit time revealed higher tumor-to-pancreas contrast than did a fixed scan delay, and tumor conspicuity was better. This means that with 16-section CT, increased contrast material flow rate of 8 mL/sec and individualized scan delay were associated with improved pancreatic enhancement and tumor-to-pancreas contrast compared with flow rate of 4 mL/sec and fixed scan delay [007].

The aim of one study was to compare dual-phase and single-phase helical CT for the detection and assessment of resectability of pancreatic adenocarcinoma. It was studied 60 patients (31 men, 29 women; age range, 31-84 years; mean age, 62 years) with suspected pancreatic malignancy. Patients were randomly assigned to one of two groups. For group A (n=30), unenhanced scans through the liver and pancreas were followed by two separate acquisitions (dual-phase) at 20-25 and at 60-80 sec after intravenous contrast administration. For group B (n=30), unenhanced scans were followed by one set of scans (single-phase) acquired caudocranially (from the inferior hepatic margin to the diaphragm) starting 50 sec after intravenous contrast administration. Two observers independently scored images for the presence of tumor and for assessment of tumor resectability. Comparison of dual-phase versus single-phase helical CT for tumor detection showed a diagnostic accuracy for observer 1 of 87 percent and 90 percent, respectively, and for observer 2, of 90 percent and 87 percent, respectively. For both helical CT techniques, the overall agreement between the two observers was 83 percent for single-phase helical CT and 90 percent for dual-phase helical CT. The assessment of resectability was affected by the low number of resectable tumors (n=8). The authors concluded that single-phase helical CT is effective for the

diagnosis and assessment of resectability of patients with suspected pancreatic carcinoma. Advantages are the lower radiation dose and fewer images to film and store [008].

Iodine concentration

The purpose of another study was to determine the influence of two different iodine concentrations of the non-ionic contrast agent, Iomeprol, on contrast enhancement in multislice CT (MSCT) of the pancreas. To achieve this MSCT of the pancreas was performed in 50 patients with suspected or known pancreatic tumours. The patients were randomly assigned to group A (n=25) or group B (n=25). There were no statistically significant differences in age, height or weight between the patients of the two groups. The contrast agent, Iomeprol, was injected with iodine concentrations of 300 mg/ml in group A (130 ml, injection rate 5 ml/s) and 400 mg/ml in group B (98 ml, injection rate 5 ml/s). Arterial and portal venous phase contrast enhancement of the vessels, organs, and pancreatic masses were measured and a qualitative image assessment was performed by two independent readers. In the arterial phase, Iomeprol 400 led to a significantly greater enhancement in the aorta, superior mesenteric artery, coeliac trunk, pancreas, pancreatic carcinomas, kidneys, spleen and wall of the small intestine than Iomeprol 300. Portal venous phase enhancement was significantly greater in the pancreas, pancreatic carcinomas, wall of the small intestine and portal vein with Iomeprol 400. The two independent readers considered Iomeprol 400 superior over Iomeprol 300 concerning technical quality, contribution of the contrast agent to the diagnostic value, and evaluability of vessels in the arterial phase. No differences were found for tumour delineation and evaluability of infiltration of organs adjacent to the pancreas between the two iodine concentrations. In conclusion the higher iodine concentration led to a higher arterial phase contrast enhancement of large and small arteries in multislice CT of the pancreas and therefore improves the evaluability of vessels in the arterial phase [009].

Hyoscyamine

Among 50 patients referred for helical computed tomography (CT) of the pancreas, 24 randomly selected patients received 40 mg of hyoscyamine butylbromide to evaluate whether its administration improved image quality and diagnostic findings. Differences between the groups were not statistically significant. It was therefore concluded that hyoscyamine butylbromide does not contribute a diagnostic advantage at helical CT of the pancreas [010].

Contrast injection rate

The purpose of another study was twofold: to compare pancreatic enhancement obtained after high and low rates of intravenous injection of contrast medium and to compare image quality between helical and dynamic sequential CT examinations of the pancreas using optimized scanning parameters. One hundred patients were randomly allocated to undergo either a helical CT (HC) acquisition after contrast injection at 6 ml/sec or a dynamic sequential CT (DS) acquisition after contrast injection at 2 ml/sec. Both ionic and nonionic contrast material were used in each group. Pancreatic attenuation values were measured on each section in each patient and averaged for each group. Image quality and visualization of anatomic landmarks were scored by two independent reviewers who were blinded to the acquisition technique. Mean pancreatic enhancement was significantly higher in the helical CT (61 $\pm$17 H) than in the dynamic group (54 $\pm$ 17 H). Peak pancreatic enhancement was similar in the HC (74 $\pm$ 19 H) and DS (74 $\pm$ 17 H) groups. In the HC group, the optimal pancreatic enhancement index was 47 percent versus 35 percent for the DS group. The time to peak enhancement was 39 sec in the HC group and 71 sec in the DS group. The optimal scanning interval was 13 sec in the HC group versus 21 sec in the DS group. Image quality

was not significantly different between the protocols, but misregistration and motion artifacts were fewer on HC examinations. Image quality was similar with both protocols [011].

To assess the effects of the intravenous injection rate and dose of contrast material on pancreatic computed tomography (CT) a total of 126 patients were divided at random into four groups with different injection rates and doses. Groups 1 and 2 underwent injection of 2 mL per kilogram of body weight of 300 mg of iodine per milliliter of contrast material, and groups 3 and 4 underwent injection of 1.5 mL/kg. The injection rate was 5 mL/sec for groups 1 and 3 and 3 mL/sec for groups 2 and 4. Single-level serial CT scanning was performed at the level of the pancreatic head, and the pancreatic enhancement value was calculated. The maximum pancreatic enhancement value was 99 HU $\pm$ 18 (mean $\pm$ SD) for group 1, 90 HU $\pm$ 18 for group 2, 86 HU $\pm$ 15 for group 3, and 74 HU $\pm$ 13 for group 4. There were significant differences in the maximum pancreatic enhancement value between groups 1 and 2, between groups 3 and 4, between groups 1 and 3, and between groups 2 and 4. This means that both a higher dose and a faster injection rate increased the maximum pancreatic enhancement value [012].

Magnetic resonance imaging

To compare image quality in magnetic resonance cholangiopancreatography (MRCP) performed with and without oral application of ferrous gluconate, Lösferron®, a prospective study compares MRCPs performed on 52 patients with a 1.5 T clinical whole body scanner using a standard body coil. After randomization, patients ingested either 0.5 l of Lösferron® (n=27, group 1) or no oral contrast agent (n=25, group 2) prior to the examination. 7 RARE (40 to 20 degrees) sequences were obtained, followed by selected 3 mm HASTE (T 2 - weighted with fat suppression) sequences. After blinding, image quality was rated by two radiologists using a scale of 1 (not discernible) to 5 (very well discernible). The oral application of ferrous gluconate was well tolerated by all patients, and all sequences could be acquired and evaluated in all 52 patients. For the different sections of the biliary system, the mean ratings with and without Lösferron were, respectively, 3.3 and 3.4 for the left hepatic duct, 3.3 and 3.3 for the right hepatic duct, 3.5 and 4.0 for the extrahepatic bile duct, and 2.8 and 3.5 for the intrapancreatic bile duct. The corresponding ratings for the pancreatic duct were 2.8 and 3.2 for the pancreatic head, 2.8 and 3.4 for the pancreatic body, and 2.7 and 3.2 for the pancreatic tail. The differences with and without contrast agent were not statistically significant. Interobserver variability was between 0.37 for the pancreatic duct in the tail of the pancreas and 0.66 for the right hepatic duct. The authors concluded that despite the trend toward a better rating of the image quality for all sections of the pancreaticobiliary ductal system with ferrous gluconate, a significant difference was not found in any ductal section after correction for multiple testing [013].

ERCP

Low-osmolar contrast medium

To evaluate whether a low-osmolar contrast medium could decrease hyperamylasemia after endoscopic retrograde pancreatography, a prospective randomized double-blind trial of 54 consecutive patients with suspected pancreatic disease referred for endoscopic retrograde pancreatography was performed. The low-osmolar contrast medium iohexol and high-osmolar amidotrizoate were used. No statistically significant differences with regard to rise in pancreatic-type amylase, pain reaction, or diagnostic information were found. No case of acute pancreatitis was observed [014].

ERCP versus PTC

In a study published 1976, 66 consecutive patients, who were deeply jaundiced or in whom intravenous cholangiography had failed, were randomized to retrograde endoscopic cholangiography or percutaneous transheptic cholangiograhy with the "skinny" Chiba needle technique. Twenty-eight patients were assigned to retrograde cholangiography, which succeeded in 17 (65 %). Percutaneous cholangiography was successful in 16 (50 %) of the remaining 32 patients. When patients in whom the first procedure was unsuccessful were reinvestigated by the alternative technique, retrograde cholangiograms were obtained in 13 (81 %) of 16, and percutaneous cholangiograms in 8 (73 %) of 11. Thus, one or the other technique was successful in 54 (90 %) of 60 patients. When the results were analyzed separately for extrahepatic (29 patients) or intrahepatic (31 patients) cholestasis, percutaneous cholangiography was successful in 95 percent of patients with extrahepatic cholestasis but in only 25 percent with intrahepatic cholestasis. Endoscopic retrograde cholangiography successed in 63 percent of patients with extrahepatic and 76 percent with intrahepatic causes of cholestasis. Complications occurred only in patients with extrahepatic cholestasis. Cholangitis and septicemia occurred in 1 patient after retrograde cholangiography and in 2 after the percutaneous technique. An intraperitoneal bile leak occurred in one other patient after percutaneous cholangiography [015].

> *Comment: Time has proven that ERCP is the primary modality for managing jaundice in these patients, not least due to the pattern of complications for ERCP and PTC.*

Brush cytology

Cancer detection rates with biliary brush sampling remain disappointingly low. A low cellular yield is often the limiting factor in making a diagnosis of malignancy. The new Cytolong brush (Cook Endoscopy) is 3 mm in diameter, 5 cm long, with stiffer bristles oriented at 45 degrees on a 7F sheath. It was hypothesized that this new brush might improve cancer detection rates by increasing cellular yield and patients found to have a biliary stricture suspicious for neoplasia on ERCP were randomized to undergo brush sampling for cytology with a standard brush or the Cytolong brush. Repeat sampling was then performed with the other brush. Stricture dilation was not performed prior to brushing. Specimen results were considered normal, atypical (considered benign), highly atypical (suspicious for cancer), or malignant. All specimens were assigned a cellularity score (0 to 3, insufficient to excellent). Final diagnosis was based on cytologic results plus surgery, EUS, autopsy, or clinical follow-up. From 2001 to 2003, 102 patients had specimens obtained from 94 malignancies (47 % pancreatic cancer). The cancer detection rate was 25 of 94 (27%) using CB and 28 of 94 (30 %) with the standard brush. No patient had positive cytology results with CB and negative cytology results with the standard. Cancer detection rates of 28 percent (18 of 64) and 31% (20 of 64) were found for the two methods, respectively, in distal biliary strictures, and 23 percent (7 of 30) and 27 percent (8 of 30) in proximal strictures. This means that despite improved cellularity, cancer detection rates were not improved by using the larger Cytolong brush in this study [016].

> *Comment: There is a value of a positive answer on a biliary brush sampling, but still many years after the introduction of the technique the negative predicting value is almost nil.*

ENDOSCOPIC STENTING

Patency and costs of different stents

Tannenbaum stent

Stent clogging is the major limitation of palliative treatment for malignant biliary obstruction. Metal stents have much better patency than plastic stents, but are more expensive. Preliminary data suggest that the designed plastic stent (Tannenbaum) has better duration of patency than the polyethylene stent. One study aimed to compare the efficacy and cost effectiveness between the Tannenbaum stent without side holes and the uncovered metal stent for patients with malignant distal common bile duct obstruction. In the study, 47 patients (median age, 73 years, 56-86 years) with inoperable malignant distal common bile duct strictures were prospectively randomized to receive either a Tannenbaum stent (n= 24) or an uncovered self-expandable metal stent (n=23). The two groups were comparable in terms of age, gender, and diagnosis. The median first stent patency was significantly longer in the metal group than in the Tannenbaum stent group (255 vs 124 days). There was no significant difference in survival between the two groups. The total cost associated with the Tannenbaum stents was significantly lower than for the metal stents (17,700 vs 30,100 euros), especially for patients with liver metastases (3,000 vs 6,900 euros). The authors concluded that metal stent placement is an effective treatment for inoperable malignant distal common bile duct obstruction, but Tannenbaum stent placement is a cost-saving strategy, as compared with metal stent placement, especially for patients with liver metastases and expected short survival time [017].

A pilot study suggested improved duration of patency of the Tannenbaum stent compared with polyethylene stents. The aim of one prospective, multicenter randomized trial was therefore to compare the Tannenbaum Teflon stent with a conventional polyethylene endoprosthesis (Cotton-Leung biliary stent set) for the treatment of malignant biliary strictures. Patients over age 18 years with symptoms caused by nonhilar malignant biliary strictures were enrolled. Patients were randomized to receive a 10F Tannenbaum or polyethylene stent after a guidewire was passed beyond the stricture. One hundred six patients (mean age 72 years and 71 years, respectively) were enrolled (54 Tannenbaum, mean age 72 years; 52 polyethylene, mean age 71 years). Tannenbaum and polyethylene stent placement was successful in, respectively, 100 percent and 96 percent of procedures without complications. The mean (SD) 90-day stent patency of the Tannenbaum stent was 67 percent (7 %) compared with 73 percent (7 %) for the polyethylene stents. The author concluded that the study demonstrated no difference in ease of implantation or stent patency between Tannenbaum and polyethylene stents [018].

Preliminary studies suggested improved duration of patency of a Tannenbaum design stent with a stainless steel mesh and an inner Teflon coating. It was now compared the patency of these stent (n=30) with a conventional polyethylene stent (n=30) in a prospective randomized trial in 1998 in patients with distal malignant bile duct obstruction. Diagnosis included carcinoma of the pancreas (n=57) and ampullary cancer (n=3). There were 29 men and 31 women with a median age of 77 years. Stent diameter (10 Fr) and length (11 cm) were similar but both stent design and material were different: a Tannenbaum design stent with a stainless steel mesh and an inner Teflon coating, and an Amsterdam-type PE stent. Early complications occurred in two patients in each group. Stent dysfunction occurred in 18 of in the first type of stents and 12 in the second type. Median stent patency was 102 days and 142 days, respectivel – a not significant difference. Median survival did not differ significantly for both treatment groups (121 days and 105 days, respectively). Stent migration, in all cases proximal into the common bile duct, occurred in four patients in the Tannenbaum design stent with a stainless steel mesh and an inner Teflon coating group versus zero in the

polyethylene group, which reached statistical significance. The authors concluded that the study did not confirm improved patency of Tannenbaum-type Teflon-coated stents. Proximal migration prompts for additional design modifications [019].

The aim was in one study to compare the clinical efficacy of the Tannenbaum (TB) biliary prostheses, a recently designed Teflon stent without side holes, with the Cotton-Huibregtse (CH) polyethylene stent. Fifty-seven patients (26 men, mean age 76 years) with unresectable malignant tumors and distal biliary stenosis were included (38 pancreatic head cancer, 17 cholangiocarcinoma, 2 ampullary cancer). Patients were prospectively randomized to have a 10F, 7 cm long TB (29 patients) or CH (28 patients) stent inserted endoscopically. Four patients (2 TB and 2 CH) were excluded: 3 because of the failure of stent insertion and 1 because of a protocol violation. The patients were evaluated clinically and, if necessary, with biochemical tests every month until death or until they needed surgery for symptoms of gastric outlet obstruction. When occlusion or dislocation occurred, the stent was replaced with one of the same type. The two groups were comparable in mean age, gender, and diagnosis. The patients were followed for a mean of 145 days (range 24 to 613); by the end of the study 47 patients (81 %) had died or developed symptoms of gastric outlet obstruction. Median survival was 88 days (range 24 to 613) in the TB group and 76 days (23 to 486) in the CH group. Stent exchange (occlusion 16, dislocation 3) was necessary for 5 patients in the TB group and 7 in the CH group. No statistical difference was found on comparing the mean duration of function of the first, second, and third stents. The median duration of stent function was 96 days (range 11 to 613) in the TB group and 76 days (range 23 to 323) in the CH group. No significant difference was found in either survival time or stent patency. This means that the study found no significant advantage of the Tannenbaum prostheses over the standard polyethylene stent in the palliation for patients with distal malignant biliary stenosis with regard to survival or length of stent patency [020].

> Comment: The four randomized trials of the Tannenbaum stents are all limited in size and each could detect only large differences. Such differences could not be found.

Self-expandable metal stents

Covered self-expandable metal stents (EMS) were developed to overcome tumour ingrowth in conventional EMS. It was enrolled 112 patients with unresectable distal biliary malignancies. They were randomly assigned to polyurethane covered (n=57) or original diamond stent (n=55). Stent occlusion occurred in eight patients (14 %) after a mean of 304 days in the covered group, and in 21 patients (38 %) after a mean of 166 days in the uncovered group. The incidence of covered EMS occlusion was significantly lower than that of uncovered EMS. The cumulative stent patency of covered stents was significantly higher than that of uncovered stents. No tumour ingrowth occurred in the covered group while it was observed in 15 patients in the uncovered group. In subgroup analysis, the cumulative patency of the covered EMS was significantly higher in pancreatic cancer and metastatic lymph nodes. There was no significant difference in survival between the two groups. Acute cholecystitis was observed in two of the covered group and in none of the uncovered group. Mild pancreatitis occurred in five of the covered group and in one of the uncovered group. The authors concluded that covered diamond stents successfully prevented tumour ingrowth and were significantly superior to uncovered stents for the treatment of patients with distal malignant biliary obstruction. However, careful attention must be paid to complications specific to covered self-expandable metal stents, such as acute cholecystitis and pancreatitis [021].

The industry standard since 1990 for self-expanding biliary metallic stents has been the Wallstent. In 1998 the Spiral Z-stent was released. Now a randomized trial compared the Z-stent with the Wallstent in the treatment of malignant biliary obstruction in patients with

unresectable malignant biliary obstruction distal to the bile duct bifurcation. Patients were randomized to receive a 10-mm diameter Wallstent or a 10-mm diameter Z-stent. A total of 145 patients were randomized; 13 were excluded. Sixty-four patients who received a Z-stent and 68 who had a Wallstent are included in the analysis. Tumors responsible for bile duct obstruction were pancreatic cancer (108), cholangiocarcinoma (15), metastatic cancer (6), and papillary cancer (3). Metallic stents were successfully placed in all patients. Seven technical problems were encountered during placement of the Z-stent and 5 with the Wallstent. There were 21 occlusions requiring reintervention (8 Z-stent, 13 Wallstent; a not statistically significant difference). Median time to reintervention was the for Z-stent 162 days and for Wallstent 150 days. The overall calculated median patency rates were for Z-stent 152 days and for Wallstent 154 days [022].

To compare percutaneous self-expanding metal stents with conventional endoscopic polyethylene endoprostheses for treatment of malignant biliary obstruction by means of a prospective randomized clinical trial, patients with biliary obstruction due to inoperable primary carcinoma of the pancreas, gallbladder, or bile ducts or regional lymph node metastases were included. Evaluated outcomes included technical and therapeutic success rates, morbidity and 30-day mortality rates, hospital stay length and readmission, biliary reobstruction, and overall survival rates. Data were analyzed according to both the intention-to-treat principle. After randomization, 28 patients were assigned to receive a percutaneous self-expanding metal stent and 26 patients to receive a 12-F endoscopic polyethylene prosthesis. The technical success rates of both implantation procedures were similar (percutaneous, 75 %; endoscopic, 58 %), whereas therapeutic success was significantly higher in the percutaneous group (71 % vs 42 %). However, major complications were more common in the percutaneous group (61 % vs 35 %) but it did not reach statistical significance and did not account for differences in 30-day mortality rates (percutaneous, 36 %; endoscopic, 42 %). Overall median survival was significantly higher in the percutaneous group than in the endoscopic group (4 vs 2 months). Cox regression analysis enabled identification of placement of the percutaneous self-expanding metal stent as the only significant, independent predictor of survival (relative risk, 2.19; 95 % confidence interval 1.1 to 4.3) [023].

Although metallic stents remain patent longer than plastic stents, the optimal palliation of inoperable malignant biliary strictures remains controversial because of the high cost of metallic stents and short patient survival. A total of 101 patients (mean age 73 years) with malignant strictures of the common bile duct were included in this study, after three exclusions for technical failure (n=3) and one for noncompliance with study design. The etiology of the strictures included pancreatic cancer (n=65), cholangiocarcinoma (21), ampullary tumor (3), and metastatic lymph nodes (12). Patients were randomized to receive either an 11.5F polyethylene stent to be exchanged in case of dysfunction (group 1, n=33), an 11.5F stent to be exchanged every 3 months (group 2, n=34), or a self-expanding metallic Wallstent (group 3, n=34). Endoscopic procedures were successful (including complete relief of jaundice) in 97 percent of cases. Procedure-related morbidity was 12 percent, and mortality was 2.9 percent. Bilirubinemia after 48 hours (37 % $\pm$ 22 % decrease from the preoperative level) did not differ between groups. Patients were followed for a mean of 166 days (median 143, range 0 to 596 days). Overall survivals were not different between groups, but complication-free survival for groups 2 and 3 was significantly longer than that of group 1. Cumulated hospital days were 7 $\pm$ 2, 11 $\pm$ 2, and 6 $\pm$ 1 (groups 1, 2, and 3, respectively) which was significant differences. Cost analysis showed that metallic stents were advantageous in patients surviving more than 6 months, whereas a plastic stent was advantageous in patients surviving 6 months or less [024].

Migration and clogging are frequent problems with conventional endoprostheses. It was in Germany investigated if expandable metal stents offer improved palliation compared to conventional stents. Sixty-two patients with common bile duct lesions were randomized to

receive polyethylene or metal stents. Stents were placed endoscopically or by the combined percutaneous-endoscopic route. Early results (< 1 month) were similar in both groups. Long-term follow-up (n=28 polyethylene, median: 5 months; n=27 metal, median: 5 months) showed a higher stent failure rate in the polyethylene (n=12; 43 %) compared to the metal group (n=6; 22 %). The incidence of cholangitis was significantly higher in the polyethylene (n=10; 36 %) compared to the metal group (n=4; 15 %). Life-table analysis showed a significantly reduced incidence of stent failure in the metal stent compared to the polyethylene group. The total duration of hospital stay for treatment of stent related problems was significantly higher in the polyethylene (12 $\pm$ 3 days) compared to the metal group (4 $\pm$ 2 days). The costs for retreatment because of stent failure were significantly higher in the plastic (DM 5900 $\pm$ 1516) compared to the metal group (DM 2070 $\pm$ 977). As a result, the overall costs (treatment of stent related complications & stents) were higher in the polyethylene group (DM 6000 $\pm$ 1500) [025].

Most patients with malignant common bile duct strictures are suited only for palliation of jaundice by placement of a polyethylene (PE) stent using an endoscopic retrograde cholangiographic technique. Occlusion of these stents occurs after 3 to 4 months, whereas uncovered self-expanding metal stents (SEMS) remain open twice as long. The initial higher cost of the latter might be balanced by a decreased need for repeat intervention. To compare the patency of 10F PE stents and covered 30F steel SEMS (Wallstent; Boston Scientific) a single-center, prospective, randomized, controlled trial was performed in non-referred patients with unresectable malignant common bile duct strictures. Fifty-one and 49 patients were allocated to the PE stent and SEMS groups, respectively. Fifty-six patients died without stent failure within 10 months (median, 3 months). Twenty-two PE stent and 9 SEMS patients developed failure after a median of 1 and 4 months, respectively, which was a significant difference. Median patency times were 2 and 4 months in the PE and SEMS groups, respectively, which was a significant difference. Median survival was 5 months; in 35 patients with distant metastases, the median survival was 3 months (PE group, 2 months). The authors concluded that the more-effective SEMS should be recommended in unresectable patients with malignant common bile duct strictures, who survive a median of longer whereas less costly plastic stents are preferable in the one third of patients who have distant metastases [026].

> *Comment: It is now well documented that metallic stents are advantageous in patients surviving more than 6 months, whereas a plastic stent is advantageous in patients surviving 6 months or less*

Double-layer stent

The aim of one study was to carry out a prospective comparison of two stents with different materials and shapes: the Olympus DoubleLayer stent (DLS; perfluoro alkoxy, without sideholes) and the standard polyethylene stent with sideholes. A total of 120 patients (70 women; mean age 71, range 36-91) with jaundice due to malignant strictures of the middle to distal third of the common bile duct were randomly assigned to receive either DLS (n=60) or polyethylen (n=60) biliary stents. Patients with cholangitis, hemobilia, previous biliary drainage, hilar stricture, or ampullary cancer were excluded. In all, 28 DLS patients (47 %) and 17 polyethylen stent patients (29 %) died without clinical evidence of stent occlusion after a mean of 114 and 105 days, respectively, which was a significant difference. Twenty-six DLS patients (43 %) and 38 polyethylen stent patients (63 %) had symptoms of stent clogging after a mean of 144 and 99 days, respectively, again a significant difference. Stent dysfunction (stent orifice impacted on the bile duct or duodenal wall, stent migration) was recorded in six DLS patients (10 %) and five polyethylen patients (8 %). Kaplan-Meier analysis of stent clogging-free survival showed a significantly longer patency period with the DLS stents. These results show that DoubleLayer stents have a longer patency period than

polyethylen stents. Patients who received polyethylen stents had a higher risk of stent occlusion (relative risk 3.1; 95 % CI, 1.6-5.9) before death than DLS patients [027].

Polyurethane stent

A hypothesis is that due to the less porousness of the polyurethane surface, there might be lesser adherence and consequently a later occlusion. Thirty-eight patients in two groups of 19 were evaluated prospectively and at random as they were treated for biliary tract obstruction due to inoperable tumors. Biliary endoprosthesis (plastic standard or polyurethane 10 French diameter) were placed, according to the randomization, after a previous staging with clinical examination, laboratory analysis and images. The follow-up with the same parameters was monthly done. Twelve of the 38 patients were female and the average age 63 (range 81-49). The stents were placed in 17 patients with biliary cancer, 14 pancreatic cancer, 2 papillary cancer, 2 gallbladder cancer with bile duct invasion and 3 liver metastasis with biliary tract compression. The clinical and laboratory parameters in 36 patients at 30 days improved. On the contrary, 2 (1 plastic standard and 1 polyurethane stent) did not improve. There were 29 deaths due to the basic illness and not related to the endoscopic method. A renewed obstruction occurred at 13 weeks (range 4-32) in the standard stents and 12 (range 2-24) in the polyurethane ones. This means that there were no significant differences in the two groups of patients [028].

Hydromer-coated polyurethane stents (HCPS) have a low coefficient of friction that may reduce sludge formation and potentially increase stent longevity. Eighty-three patients (39 men, mean age 69 years) with malignant mid or distal bile duct strictures were prospectively randomized to receive either 10F HCPS (n=40) or standard polyethylene stents (n=43). Fifteen patients (18 %) underwent surgery after stent insertion. Six patients were lost to follow-up (7 %), whereas 34 died of the underlying disease without evidence of stent occlusion (15 HCPS group and 19 polyethylene group). Median survival was 75 days (range 15 to 372 days) and 108 days (range 25 to 325 days) in the HCPS and polyethylene stent groups, respectively, which was not significant statistically. Stent occlusion was observed in 25 patients (42 %), 16 with HCPS stents and 9 with polyethylene stents, with a median patency of 103 days (range 40 to 280 days) and 68 days (range 32 to 175 days), respectively, again not significant. This means that HCPS do not appear to provide significant clinical advantages in terms of stent longevity over standard plastic prostheses [029].

Placement of stents with respect to the sphincter of Oddi

Placement of stents above an intact sphincter of Oddi might prevent migration of bacteria and deposition of organic material into the stent. In patients with malignant obstructive jaundice prolongation of function time of the stent would be expected if it is placed above the sphincter of Oddi. Thirty-four patients were randomized to stent placement either above (n=17) or across (n=17) the sphincter of Oddi. Straight 10F gauge Teflon stents were used. The patients were evaluated clinically and biochemically at monthly intervals during follow-up. The median stent function time (i.e. the time from insertion of the stent until stent replacement, patient death, or study termination) were 110 days (25th to 75th percentiles, 61 to 320 days) for stents placed above the sphincter of Oddi and 126 days (25th to 75th percentiles, 89 to 175 days) for stents placed across the sphincter of Oddi, which was a nonsignificant difference. Stent replacement rates were 59 percent (10 of 17) in patients with stents placed above the sphincter and 29 percet (5 of 17) in patients with stents placed across the sphincter, which also was a not significant difference. Significantly more patients in the former group experienced stent migration (9 vs 2). The median time from stent insertion until replacement of the stents placed above and across the sphincter of Oddi were 82 days (25th to 75th percentiles, 31 to 185 days) and 89 days (25th to 75th percentiles, 13 to

150 days), respectively. This means that no significant difference in overall stent performance between the two groups was found, although more stents placed above the sphincter of Oddi migrated [030].

Need of sphincterotomy

Considerable controversy surrounds the adoption of endoscopic sphincterotomy (ES) to facilitate the placement of 10F plastic stents and to reduce the risk of pancreatitis. From 1996 to 2001, therefore 172 consecutive patients, who underwent placement of a single 10F-polyethylene stent for inoperable malignant strictures of the common bile duct, were randomly assigned to 2 groups. In group A (96 patients), a ES was performed before stent placement. In Group B, 96 patients had stent inserted directly. Early complications (within 30 d) and late effects (from 30 d to stent replacement) were assessed. Stent insertion was successful in 96 percent of the patients in group A and in 94 percent of the patients in group. Early complications were found in 7 percent in patients who underwent ES versus 4 percent in the controls; a not significant difference. In group A pancreatitis developed in two patients and bleeding in three; whereas pancreatitis occurred in 2 patients in group B. Complications were managed conservatively. No procedure related mortality occurred. All late complications were acute cholangitis due to stent occlusion. It was performed a stent replacement in 87 patients that was successful in 84 cases without differences between groups. The authors concluded that sphincterotomy does not seem to be necessary for placement of 10F-PS in patients with malignant common bile duct obstruction [031].

Meta-analyses

A variety of stent designs has been studied for endoscopic stenting of the bile duct in patients with malignant biliary obstruction. Although metal stents are associated with longer patency, their costs are significantly higher than plastic stents. To compare clinical outcome and cost-effectiveness of endoscopic metal and plastic stents for malignant biliary obstruction by a systematic review and meta-analysis of all randomized controlled trials in this area it was conducted searches to identify all randomized controlled trials in any language from 1966 to 2006 using electronic databases and hand-searching of conference abstracts. Seven randomized controlled trials were identified that met the inclusion criteria, and 724 participants were randomized to either metal or plastic endoscopic stents. No significant difference between the two stent types in terms of technical success, therapeutic success, 30-day mortality or complications was observed. Metal stents were associated with a significantly less relative risk of stent occlusion at 4 months than plastic stents (relative risk 0.44; 95 % confidence interval 0.30 to 0.63). The overall risk of recurrent biliary obstruction was also significantly lower in patients treated with metal stents (relative risk 0.52; 95 % confidence interval 0.39 to 0.69). The median incremental cost-effectiveness ratio of metal stents was USD 1820 per endoscopic retrograde cholangiopancreatography prevented. It was concluded that endoscopic metal stents for malignant biliary obstruction are associated with significantly higher patency rates than plastic stents as early as 4 months after insertion. Metal stents will be cost-effective if the unit cost of additional endoscopic retrograde cholangiopancreatographies per patient exceeds USD 1820 [032].

Palliative endoscopic stents or surgical by-passes are often required for inoperable pancreatic carcinoma to relieve symptomatic obstruction of the distal biliary tree. The optimal method of intervention remains unknown. To compare surgery, metal endoscopic stents and plastic endoscopic stents in the relief of distal biliary obstruction in patients with inoperable pancreatic carcinoma it was searched the databases of the Cochrane Upper Gastrointestinal and Pancreatic Group specialised register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CancerLit, Current Concepts Database and BIDS. The searches were re-run in December 2005. Reference lists of articles and published abstracts from UEGW

and DDW were hand-searched. Randomised controlled trials comparing surgery to endoscopic stenting, endoscopic metal stents to plastic stents, and different types of endoscopic plastic and metal stents, used to relieve obstruction of the distal bile duct in patients with inoperable pancreatic carcinoma. Twenty-one trials involving 1,454 people were included. Based on meta-analysis, endoscopic stenting with plastic stents appears to be associated with a reduced risk of complications (relative risk 0.60; 95 % confidence interval 0.45 to 0.81), but with higher risk of recurrent biliary obstruction prior to death (relative risk 18.59; 95 % confidence interval 5.33 to 64.86) when compared with surgery. There was a trend towards higher 30-day mortality in the surgical group (relative risk 0.58; 95 % confidence interval 0.32 to 1.04). There was no evidence of a difference in technical or therapeutic success. Other outcomes were not suitable for meta-analysis. No trials comparing endoscopic metal stents to surgery were identified. In endoscopic stent comparisons, metal biliary stents appear to have a lower risk of recurrent biliary obstruction than plastic stents (relative risk 0.52; 95 % confidence interval 0.39 to 0.69). There was no significant statistical difference in technical success, therapeutic success, complications or 30-day mortality using meta-analysis. A narrative review of studies of the cost-effectiveness of metal stents drew conflicting conclusions, but results may be dependent on the patients' length of survival. Neither Teflon, hydrourethane, nor hydrophilic coating appear to improve the patency of plastic stents above polyethylene in the trials reviewed. Only perflouro alkoxy plastic stents had superior outcome to polyethylene stents in one trial. The single eligible trial comparing types of metal stents reported higher patency with covered stents, but also a higher risk of complications. These results are based on review of the trials individual results only. The authors concluded that endoscopic metal stents are the intervention of choice at present in patients with malignant distal obstructive jaundice due to pancreatic carcinoma. In patients with short predicted survival, their patency benefits over plastic stents may not be realized [033].

> *Comment: Both meta-analyses are in favor of metal stents, but in patients with short survival the plastic stents are cost-effective. No trials comparing endoscopic metal stents to surgery were identified.*

Antibiotics and ursodeoxycholic acid for increased patency

Ciprofloxacin

In vitro experimental and animal studies have shown that quinolones reduce the adherence of bacteria on a polyethylene tube and prevent stent blockage. The aim of one study was to see whether ciprofloxacin prevents stent blockage in patients with malignant stricture of the biliary tract. Patients with inoperable biliary or pancreatic tumor not involving the bifurcation of the common hepatic duct were recruited. They were randomized to receive either endoscopic stenting alone or stenting with prophylactic treatment of ciprofloxacin (200 mg i.v. before stenting, followed by 250 mg orally twice per day). In each follow-up visit, clinical symptoms of cholangitis were documented and blood samples taken for blood counts, serum levels of bilirubin, and alkaline phosphatase. Stent blockage was defined as clinical symptom(s) of cholangitis with biochemical or radiological evidence of stent dysfunction. Fifty-eight patients were recruited into the study. Three patients in the stenting group and three in the ciprofloxacin group were excluded after randomization. Eleven patients received stenting alone and five patients receiving ciprofloxacin had previous endoscopic stenting. Thirteen patients (50 %) in the ciprofloxacin group and eight patients (31 %) in the stenting group died before stent blockage. Ten patients (38 %) in each group had stent blockage during the follow-up at 20 week. The median stent patency was 12 weeks and 12 weeks in the ciprofloxacin group and the stenting group, respectively. Kaplan-Meier analysis of stent patency showed no difference between the two groups. Among patients who received

endoscopic stenting for the first time, there was a trend favoring ciprofloxacin treatment, but the difference was not significant. The 30-day and 20-week mortality between the groups were comparable [034].

Comment: So far there is no hard evidence that antibiotics in stents are of value.

Levofloxacin and ursodeoxycholic acid

One of the main advances in biliopancreatic endoscopic therapy has been the ability to palliate patients with biliary obstruction by placement of a stent during ERCP, but this is often complicated by clogging of the stent with subsequent jaundice and/or cholangitis. Stent clogging may be caused by microbiological adhesion and biliary stasis. Therefore, the use of antibiotics and choleretic agents such as levofloxacin and ursodeoxycholic acid has been investigated to see whether they prolong stent patency. Ninety patients with strictures of the biliary tract and untreatable macrolithiasis with endoscopically inserted stents were now randomized into two groups: 49 subjects in group 1 (levofloxacin + ursodeoxycholic acid) and 41 in group 2 (ursodeoxycholic acid alone). In the patients in group 1 "stent patency in situ" was 50 percent longer than in group 2, with a lower incidence of cholangitis and hospital admittance. No adverse pharmacological effects were registered. Treatment with ursodeoxycholic acid and levofloxacin to prevent clogging of biliary stents was therefore recommended as routine practice. However, the authors also stated that prophylactic stent replacement probably is the most prudent strategy to avoid cholangitis, but no data supporting this was shown [035].

A study reported an open randomised controlled trial of cyclical antibiotics and ursodeoxycholic acid in prevention of plastic biliary stent occlusion. Seventy patients with malignant distal bile duct obstruction were randomised to either active treatment with cyclical antibiotics (ampicillin, metronidazole, ciprofloxacin) and ursodeoxycholic acid or no treatment after successful stent insertion. The two groups were well matched. The follow up was complete with stent occlusion or death being the end points. There was no difference in the incidence of stent occlusion between the two groups and the overall survival was similar. In conclusion, the study did not show any benefit of treatment with antibiotics and ursodeoxycholic acid in prolonging stent patency or improving survival [036].

Comment: It cannot be shown that ursodeoxycholic acid prolongs stent patency.

Postprocedure brachtherapy to increase patency

A study was also undertaken to investigate the value of after-loading treatment through biliary drainage and local chemotherapy embolism, radiofrequency ablation (RFA) or port catheter system (PCS) chemotherapy for treatment of malignant biliary obstruction after placement of expandable metallic stents. Forty-nine patients with malignant biliary obstruction not suitable for surgical treatment, including hepatic 25 tumors (17 with primary hepatocellular carcinoma, and 8 with metastasic carcinoma), biliary carcinoma in 11 cases, pancreatic carcinoma 6 cases, and Klastkin tumors in 7 cases. The patients were divided into four random groups. One underwent expandable metallic biliary endoprothesis (EMBE), the second underwent both EMBE and after-loading treatment, the third group underwent both EMBE and RFA, and the last underwent both EMBE and PCS. The four groups have significant difference in reobstruction rate and mortality rate. It was concluded that expandable metallic biliary endoprothesis combined with brachytherapy was more effective methods than EMBE alone [037].

Stents after ampullary endoscopic surgery

Tumors that arise in the region of the major duodenal papilla account for 5 percent of GI neoplasms and 36 percent of resectable pancreaticoduodenal tumors. There is limited published literature that addresses the safety of endoscopic excision of the papilla. Although there is consensus about prophylactic pancreatic-duct stent placement, there is little supporting prospective data. The aim of one randomized, controlled trial was to compare the rates of postsnare ampullectomy pancreatitis in patients who did/did not receive prophylactic pancreatic-duct stent placement. Nineteen consecutive patients who were to undergo en bloc snare ampullectomy were randomized to placement of pancreatic-duct stent after ampullectomy or to no stent placement. Ten patients received pancreatic stents. Postprocedure pancreatitis occurred in 3 patients in the 24 hours after endoscopy, all cases occurred in the unstented group, 33 percent versus 0 percent (stented group), which was a significant difference (p=0.02). Median peak amylase level was 3692 U/L (range 1819-4700 U/L) and median peak lipase level was 11450 U/L (range 5900-17,000 U/L). All 3 patients were hospitalized for a median of 2 days (range 1-6), and all made a complete recovery [038].

> *Comment: This is but a small study, but the results make it possible that prophylactic pancreatic stent placement in reducing postampullectomy pancreatitis. Future large-scale studies are required to confirm this benefit, and as this is a very rare procedure such a study must be multi-institutional.*

Endoscopy or surgery for jaundice preoperatively and in palliative patients?

Both endoscopic and surgical drainage procedures are effective palliative methods for malignant biliary obstruction. Surgical drainage is still preferred in developing countries due to the high cost of procuring metal biliary stents. The aim of one study was to evaluate the quality of life and the cost of care in patients with metastatic pancreatic cancer after endoscopic biliary drainage and surgical drainage in a prospective, randomized controlled trial conducted in a tertiary referral center in Brazil. Patients with biliary obstruction due to metastatic pancreatic cancer and liver metastasis, but without gastric outlet obstruction, were included in the study. Endoscopic biliary drainage with the insertion of a metal stent into the bile duct was compared with the surgical drainage procedure (choledochojejunostomy and gastrojejunostomy). Quality of life was assessed before, and 30 days, 60 days, and 120 days after the drainage procedure. The cost of drainage procedure, cost during the first 30 days and the total cost from drainage procedure to death were calculated. Of the 273 patients with pancreatic malignancy seen in the hospital between 2001 and 2004 35 patients were eligible for the study, and 30 agreed to participate in the study. Both surgical and endoscopic drainage procedures were successful, without any mortality in the first 30 days. The cost of biliary drainage procedure (US dollars 2,832 $\pm$ 519 vs 3,821 $\pm$ 1,181, p= 0.03), the cost of care during the first 30 days after drainage (US dollars 3,122 $\pm$ 877 vs 6,591 $\pm$ 711, p=0.001), and the overall total cost of care that included initial care and subsequent interventions and hospitalizations until death (US dollars 4,271 $\pm$ 2,411 vs 8,321 $\pm$ 1,821, p=0.001) were lower in the endoscopy group compared with the surgical group. In addition, the quality of life scores were better in the endoscopy group at 30 days (p=0.042) and 60 days (p= 0.05). There was no difference between the two groups in complication rate, readmissions for complications, and duration of survival. The authors concluded that endoscopic biliary drainage is cheaper and provides better quality of life in patients with biliary obstruction and metastatic pancreatic cancer [039].

The role of preoperative endoscopic drainage for patients with malignant obstructive jaundice was evaluated in a randomized controlled trial. A total of 87 patients were assigned to either

early elective surgery (44 patients) or endoscopic biliary drainage followed by exploration (43). Thirty-seven patients underwent successful stent insertion and 25 had effective biliary drainage. Complications related to endoscopy occurred in 12 patients. After endoscopic drainage significant reductions of hyperbilirubinaemia, indocyanine green retention and serum albumin concentration were observed. Patients with hilar lesions had a significantly higher incidence of cholangitis and failed endoscopic drainage after stent placement. The overall morbidity rate (18 patients versus 16) and mortality rate (six patients in each group) were similar in the two treatment arms irrespective of the level of biliary obstruction [040].

A total of 52 jaundiced elderly patients who had malignant obstruction of the distal common bile duct and who required palliative biliary decompression were randomized to receive either an endoscopically placed biliary endoprosthesis (10 French gauge) or conventional surgical bypass. Patients within the two treatment groups were well matched and 51 were followed until their death. Patients treated with endoprosthesis had a significantly shorter initial hospital stay than those treated surgically. In the long term, overall survival in the two groups was similar and jaundice was relieved in over 90 percent of patients. Despite more re-admissions to hospital for those patients treated endoscopically, the total time spent in hospital still remained significantly shorter in this treatment group compared with those subjected to surgery [041].

Summary: There is no benefit for surgical bypass compared to endoscopic stenting in the preoperative setting. Endoscopic biliary drainage is cheaper and may provide better quality of life in patients with biliary obstruction

SURGERY

Prophylaxis of complication

Gabexate mesilate, a synthetic protease inhibitor, was tested in preventing the postoperative complications of pancreatic surgery. For this purpose it was performed a pilot study based on two treatment groups, each numbering 25 patients, submitted to high-risk pancreatic resection. In the first group, all patients received a continuous infusion of gabexate mesilate 1 g/day up to postoperative day 4; the second group of patients received the same treatment plus octreotide 0.1 mg every 8 hours for 5 days after surgery. All patients were followed until discharge with clinical and instrumental investigations to detect the onset of postoperative complications. The overall incidences of an uneventful course were 40 percent (10/25) and 32 percent (8/25), respectively. This favourable trend, however, was not statistically significant [042].

Ulinastatin

Ulinastatin, an intrinsic trypsin inhibitor, has proved to be effective for the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography. The aim of one study was to assess the efficacy of ulinastatin for postoperative pancreatitis following pancreaticoduodenectomy in a randomized clinical trial. Patients undergoing pancreatico-duodenectomy were randomized to receive perioperative ulinastatin or placebo. Levels of serum amylase, drain amylase, and urine trypsinogen-2 were measured. A total of 42 patients were enrolled (20 in the ulinastatin group, 20 in the placebo group, 2 excluded). Two patients in the ulinastatin group and nine patients in the placebo group developed significant hyperamylasemia. No patient in the ulinastatin group and five patients in the placebo group developed pancreatitis, which was a significant difference. One patient in the ulinastatin group and two patients in the placebo group developed grade A pancreatic fistula. Serum amylase levels at 4 hr and postoperative days 1, 2, and 3, and drain amylase levels on days 2 and 3 were significantly lower in the ulinastatin group than in the placebo group. Prophylactic administration of ulinastatin reduced the levels of serum and drain amylase and the incidence of postoperative pancreatitis following pancreaticoduodenectomy [043].

> Comment: This is a small study and much larger studies are needed to state that trypsin inhibitors are of value to prevent postoperative pancreatitis after pancreatic resections – but the problem with postoperative pancreatitis is probably underestimated.

Preoperative biliary stenting

In investigations of the effects of preoperative biliary stents on postoperative complications after pancreaticoduodenectomy some studies have documented increased wound infection rates, while others have not. The importance of this issue rests on whether these postoperative complications are detrimental enough to not recommend preoperative chemoradiation in the treatment of pancreatic cancer. This study is in two parts: a retrospective review of patients who underwent pancreaticoduodenectomy at one hospital and a meta-analysis of published studies on the effects of preoperative biliary stents. In the retrospective portion, all patients who underwent pancreaticoduodenectomy from 1997 through 2006 were included in the study. In the retrospective portion, 181 patients were studied, with 123 (68 %) of these having preoperative biliary stents. Patients with and without stents had no significant difference in wound infection rate (20 % vs 17 %, respectively), intra-abdominal abscess rate (16 % vs 22 %), any postoperative complication (50 % vs 52 %) and in-hospital death (2.4 % vs 1.7 %). Fifteen studies were included in the meta-

analysis. There was variation in both the definitions of complications as well as the incidence of all postoperative endpoints among the studies. For peri-operative mortality and wound infection rate, the relative difference favored the no stent group by 0.5 percent (95 % confidence interval -0.4 % to 1.4 %) and 5.8 percent (95 % confidence interval 3.6 % to 8.0 %), respectively. For intra-abdominal abscess and overall morbidity rate, the relative difference favored the stent group by 2.0 percent (95 % confidence interval: -0.3 % to 4.3 %) and 0.06 percent (95 % confidence interval -3.8 % to 3.9 %), respectively. It was concluded that although the use of a preoperative biliary stent increases the postoperative wound infection rate by about 5 percent, there is no overwhelming evidence that it either promotes or protects from the other complications. As there was variation in the definitions used in these studies, a more uniformed system of complication reporting is required [044].

Pancreaticoduodenectomy is the only potentially curative treatment for peripapillary pancreatic tumors. However, postoperative morbidity and mortality are high, and different approaches have been tried to improve results, such as preoperative biliary drainage in patients with jaundice. One meta-analysis investigated the effect on postoperative outcome of preoperative biliary drainage by endoscopic biliary stent placement in patients who are jaundiced and who have peripapillary pancreatic tumors. A Medline search for the period 1985 to 2001 was performed. Eight retrospective studies and 2 prospective randomized controlled trials were included. Selection criteria for the primary analysis were as follows: patients with peripapillary pancreatic cancer, endoscopic stent placement versus no stent, radical surgery, and assessment of postoperative morbidity and mortality. A secondary analysis included both radical and palliative surgery. In the primary analysis, 337 patients underwent preoperative endoscopic biliary stent placement, and 412 patients had no endoscopic biliary stent placement (controls). The overall odds ratio for postoperative complications (stent vs no stent) was estimated as 0.79: (95 % confidence interval 0.36 to 1.73) and the estimated odds ratio for postoperative mortality was 0.81 (95 % confidence interval 0.33 to 1.99). In the secondary analysis, 1008 patients underwent preoperative endoscopic stenting versus 720 control patients. The odds ratio for postoperative complications in this analysis was 0.93 (95 % confidence interval 0.65 to 1.33) and for postoperative mortality is 1.12 (95 % confidence interval 0.62 to 2.01). It was concluded that no evidence was found of either a positive or adverse effect of preoperative endoscopic biliary stent placement on the outcome of surgery in patients with pancreatic cancer [045].

> Comment: It is possible that the use of a preoperative biliary stent increases the postoperative wound infection rate by in a few percent of cases, but there is no overwhelming evidence that it either promotes or protects from the other complications. It is probable that the use of stent has more to do with logistics than with infections – if the pancreatic resection cannot be performed in due time with regard to negative impact on the liver function a preoperative biliary stent should be used, otherwise not.

Standard Whipple versus pylorus-preserving pancreatoduodenectomy

Resectable carcinoma of the head of the pancreas can be treated with either standard (the Whipple) or pylorus-preserving pancreaticoduodenectomy (PPPD). From 1994 to 2002 a prospective randomized comparison between the Whipple procedure and PPPD done by the same surgeon for the patients with carcinoma of the head of the pancreas was conducted. Thirty-six patients diagnosed as pancreatic head adenocarcinoma were randomized to receive either the Whipple procedure or a PPPD. Three patients initially randomized to have a PPPD were converted to the Whipple procedure due to gross duodenal involvement. Finally, 19 patients received the Whipple procedure, 14 patients underwent PPPD and three patients had conversion. Two perioperative deaths in the Whipple group and one perioperative death in PPPD resulted in an 8 percent mortality rate in the 36 patients. Median

duration of the Whipple operation was 265 (range 203-475) min with a median blood loss of 570 (50-8540) mL. In the patients who had PPPD, median operating time was 232 (range 165-270) min, and median blood loss was 375 (range 100-1300) mL. There was one minor leak from the pancreaticojejunostomy in each group, resulting in a 6 percent minor leak in 36 patients. These outcomes were not significantly different. Delayed gastric emptying was observed more frequently after PPPD (six of 14 patients) than after the Whipple procedure (none of 19 patients) (P < 0.05). There was no significant difference between the Whipple procedure and PPPD in terms of median survival and 5-year survival rate. The median survival time was 16 months and 5-year survival rate was 9 percent in the 36 patients. Blood loss during operation influenced the prognosis. There was no significant difference between the Whipple procedure and PPPD for the treatment of pancreatic head cancer in terms of operating time, blood loss, operative mortality and long-term survival. But delayed gastric emptying was more frequently encountered in PPPD than in the Whipple procedure [046].

A prospective randomized multicenter study was performed to assess whether the results of pylorus-preserving pancreaticoduodenectomy (PPPD) equal those of the standard Whipple operation, especially with respect to duration of surgery, blood loss, hospital stay, delayed gastric emptying (DGE), and survival. PPPD has been associated with a higher incidence of delayed gastric emptying, resulting in a prolonged period of postoperative nasogastric suctioning. Another criticism of the pylorus-preserving pancreaticoduodenectomy for patients with a malignancy is the radicalness of the resection. On the other hand, PPPD might be associated with a shorter operation time and less blood loss. A prospective randomized multicenter study was performed in a nonselected series of 170 consecutive patients. All patients with suspicion of pancreatic or periampullary tumor were included and randomized for a SW or a PPPD resection. Data concerning patients' demographics, intraoperative and histologic findings, as well as postoperative mortality, morbidity, and follow-up up to 115 months after discharge, were analyzed. There were no significant differences noted in age, sex distribution, tumor localization, and staging. There were no differences in median blood loss and duration of operation between the two techniques. DGE was observed equally in the two groups. There was only a marginal difference in postoperative weight loss in favor of the standard Whipple procedure. Overall operative mortality was 5.3 percent. Tumor positive resection margins were found for 12 patients of the standard Whipple group and 19 patients of the PPPD group, a not significant difference. Long-term follow-up showed no significant statistical differences in survival between the 2 groups. This means that pylorus-preserving pancreaticoduodenectomy and standard Whipple operations were associated with comparable operation time, blood loss, hospital stay, mortality, morbidity, and incidence of delayed gastric emptying. The overall long-term and disease-free survival was comparable in both groups. Both surgical procedures are equally effective for the treatment of pancreatic and periampullary carcinoma [047]

Yet another prospective randomized trial was undertaken to compare the results of pylorus-preserving duodenopancreatectomy and classical Whipple procedures in the resection of pancreatic and periampullary tumours. Clinical data, histological findings, short-term results, survival and quality of life of all patients having surgery for suspected pancreatic or periampullary cancer between 1996 and 2001 were analysed. Two hundred and fourteen patients were randomized to undergo either a standard or a pylorus-preserving Whipple resection. After exclusion of 84 patients on the basis of intraoperative findings, 130 patients (66 standard Whipple operation and 64 pylorus-preserving resection) were entered into the trial. Of these, 110 patients with proven adenocarcinoma (57 standard Whipple and 53 pylorus-preserving resection) were analysed for long-term survival and quality of life. There was no difference in perioperative morbidity. Long-term survival, quality of life and weight gain were identical after a median follow-up of 63 (range 4-93) months. At 6 months, capacity to work was significantly better after the pylorus-preserving procedure (77 vs 56 %). The authors concluded that both procedures were equally effective for the treatment of pancreatic

and periampullary cancer. Pylorus-preserving Whipple resection offers some minor advantages in the early postoperative period, but not in the long term [048].

From 1994 to 2002, a prospective randomized comparison between the standard Whipple procedure and PPPD done by the same surgeon for the patients with carcinoma of the head of the pancreas was conducted. Thirty-six patients diagnosed as pancreatic head adenocarcinoma were randomized to receive either the Whipple procedure or a PPPD. Three patients initially randomized to have a PPPD were converted to the Whipple procedure due to gross duodenal involvement. Finally, 19 patients received the Whipple procedure, 14 patients underwent PPPD and three patients had conversion. Two perioperative deaths in the Whipple group and one perioperative death in PPPD resulted in an 8 percent mortality rate in the 36 patients. Median duration of the Whipple operation was 265 (range 203-475) min with a median blood loss of 570 (50-8540) mL. In the patients who had PPPD, median operating time was 232 (range 165-270) min, and median blood loss was 375 (range 100-1300) mL. There was one minor leak from the pancreaticojejunostomy in each group, resulting in a 6 percent minor leak in 36 patients. These outcomes were not significantly different. Delayed gastric emptying was observed significantly more frequently after PPPD (six of 14 patients) than after the Whipple procedure (none of 19 patients). There was no significant difference between the Whipple procedure and PPPD in terms of median survival and 5-year survival rate. The median survival time was 16 months and 5-year survival rate was 9 percent in the 36 patients [049].

> *Comment: As it is only one surgeon who has treated less than five patients a year the study should be looked upon with caution, even though it is well performed from a scientifical point of view – and the resuls are congruent with other similar studies.*

A prospective, randomized single-institution trial comparing standard pancreatico-duodenectomy, PD (including distal gastrectomy and retroperitoneal lymphadenectomy), to pylorus-preservating PD evaluated 299 patients with periampullary adenocarcinoma between 1996 and 2001. A standard Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) quality of life survey designed for hepatobiliary cancer was sent to 150 of these patients surviving pancreaticoduodenectomy. Quality of life and functional status were assessed via a series of subscale scores for physical, social, emotional, and functional well-being. A total of 105 QoL surveys (70 %) were returned and analyzed, with 55 of the patients having been randomized to the standard group and 50 to the radical group. The patients were evaluated at a mean of 2.2 years after pancreaticoduodenectomy. The two groups were statistically similar with regard to multiple parameters including age at operation (65 years), race, intraoperative blood transfusions, pathologic diagnosis and staging, and perioperative complications. The radical group had a significantly higher percentage of men (66 % vs 44 %), a longer operative time (369 minutes vs 327 minutes), and a longer postoperative length of hospital stay (14 days vs 10 days). The FACT-Hep total QoL scores were similar between the standard and radical groups: 144 versus 147, respectively. Additionally, the individual FACT-G subscale scores evaluating physical (22 vs 23), social (25 vs 24), emotional (19 vs 20), and functional well-being (21 vs 22) were comparable between the standard and radical groups. Subgroup analyses based on pathologic diagnosis (pancreatic, ampullary, distal bile duct, etc.) failed to reveal any differences in quality of life assessment between the standard and radical pancreaticoduodenectomy groups. Finally, QOL measures were similar when comparing time since operation (<2 years' follow-up vs >2 years' follow-up) and age ($\geq$ 65 years vs >65 years). Thus, these data demonstrate no differences in long-term quality of life between standard and radical resection. These results imply that no negative long-term QOL measures are associated with radical pancreaticoduodenectomy (as performed in this study) for periampullary adenocarcinoma [050].

Further, it was conducted a randomized prospective trial in a non-selected, consecutive patient series of the classical Whipple resection (cWhipple) and pylorus-preserving Whipple (ppWhipple). From 1996 to 1999 139 patients with suspicion of pancreatic or periampullary tumor were prospectively randomized to undergo either a cWhipple or a ppWhipple (intention to treat). Based on the inclusion and exclusion criteria, 93 of these patients were finally analyzed in the study. There were 51 cWhipple and 42 ppWhipple resections. There were no differences concerning age, gender, ASA classification, tumor type and stage, length of ICU- and in-hospital stay. However, the ppWhipple group had a significant shorter operation time. There was no difference in mortality and morbidity. The incidence of delayed gastric emptying was identical in both groups. For long-term follow-up, a total of 76 patients with histological proven pancreatic or periampullary carcinoma were analyzed. There was no difference in tumor recurrence and in long-term survival after a median follow-up of 1.5 years (0.1-3.5) [051].

Almost the same material has been published at the same time, but this time in an English-spoken journal and with a total of 114 patients with suspected pancreatic or periampullary tumors. Based on the inclusion and exclusion criteria, 77 of these patients were included in the final analysis. Forty had a cWhipple and 37 had a ppWhipple resection. There were no differences with regard to age, sex distribution, ASA classification, histologic classification, UICC stage, length of stay in the intensive care unit, and length of hospital stay. The ppWhipple group had a significantly shorter operative time, reduced blood loss, and fewer blood transfusions. There was no difference in mortality, but the cWhipple group showed a significantly higher total morbidity. The incidence of delayed gastric emptying was identical in both groups. For long-term follow-up, a total of 61 patients with histologically proven pancreatic or periampullary carcinoma were analyzed. There were no differences in tumor recurrence or in long-term survival at a median follow-up of 1.1 years (range 0.1 to 2.9 years) [052].

> *Comment: It seems as if a new analysis was done for the Swiss journal 4 month after the American with 25 new patients. However, the results were in principles the same, with exception for the differences concerning blood loss and blood transfusions.*

From 1994 to 1997, a prospective randomized comparison was conducted between the Whipple procedure and PPPD performed by the same surgeon with the same approach and same anastomotic fashion for periampullary cancer. After exclusion of seven patients, 31 patients were eligible for the study, 16 receiving PPPD and 15 a Whipple procedure. No significant difference in the age, gender distribution, tumour localization or staging was noted between the two groups. One operative death after PPPD and no operative death after the Whipple procedure resulted in a 3 per cent mortality rate in the 31 patients. Median duration of the Whipple operation was 235 (range 195-305) min, with a median blood loss of 500 (range 230-3100) ml and a median blood transfusion of 0 (range 0-10) units. In the patients who had PPPD, median operating time was 230 (range 170-275) min, median blood loss was 350 (range 100-1200) ml and median blood transfusion was 0 (range 0-4) units. There were two minor leaks from the pancreaticojejunostomy after the Whipple procedure and no leakage after PPPD, resulting in 6 per cent minor leakage in 31 patients. These outcomes were not significantly different. Delayed gastric emptying was observed more frequently after PPPD (six of 16 patients) than after the Whipple procedure (one of 15 patients), but this was not a statistically significant difference [053].

A single-institution randomized controlled trial was conducted to compare the results of standard whipple operation (SW) with those of pylorus-preserving pancreaticoduodenectomy (PPPD). Between 2000 and 2004, 27 patients with pancreatic or periampullary adenocarcinoma were enrolled into the study. All patients were randomly allocated to either a SW or a PPPD resection. Patients' characteristics, postoperative mortality and morbidity, and survival up to two years were compared. There were no significant differences in baseline

characteristics between the two groups of patients. There were also no significant differences in blood loss and operative time. Delayed gastric emptying (DGE) occurred more frequently in the PPPD group, but other operative complications, hospital mortality, and the length of hospital stay were similar for the two groups. There were no significant survival differences at two years after operation. Standard Whipple and PPPD were comparable in terms of operation time, blood loss, operative mortality and morbidity, and survival. Although the incidence of delayed gastric emptying was higher in the PPPD group, the hospital stay was similar for both groups. Both surgical procedures were equally effective for the treatment of pancreatic and periampullary carcinoma [054].

> *Summary: These nine studies are very convincing – the likelyhood that some important difference should appear in a new, larger study is little, and* if *some differences should be found it is probable that they would be so small that they were of little clinical significance.*

Meta-analyses

To consolidate the published evidence and compare outcomes between pancreatico-duodenectomy (PD) and pylorus preserving pancreaticoduodenectomy (PPPD) across all published comparative studies. Using meta-analytical techniques the study compared operative details, post-operative adverse events and survival following PD and PPPD. Comparative studies published between 1986 and 2005 of PD versus PPPD were included. A random effect model was employed, with significance reported at the 5 percent level. Thirty-two studies comprising 2822 patients (1335 PD and 1487 PPPD), including 5 randomized controlled trials with 421 patients (215 PD and 206 PPPD) were included. Patients undergoing PPPD were found to have smaller tumours, although no significant difference in the number of patients with stage III or IV disease existed between the groups (odds ratio 1.55), a not significant difference. Significantly decreased operating times (41.3 min) and fewer blood transfusions (-0.9 units) were observed in the PPPD group. There was no difference in post-operative complications, including pancreatic and biliary leaks or fistulae, between the two groups. It was suggested that peri-operative mortality was significantly decreased in the PPPD group (odds ratio 1.7), and overall survival was significantly better (hazard ratio 0.66), although this did not remain significant on subgroup analysis. It was concluded that both pancreaticoduodenectomy and pylorus preserving pancreaticoduodenectomy had similar peri-operative adverse events, however, in overall analysis pylorus preserving pancreaticoduodenectomy has lower mortality and improved long-term patient survival, although this was not reflected in the sub-group analysis [055].

The objective was to determine the relative effects of pylorus-preserving pancreatoduoden-ectomy (PPPD) and standard Whipple pancreaticoduodenectomy (SWPD) in patients with pancreatic or periampullary cancer. It was searched seven bibliographic databases, conference proceedings, and reference lists of articles and textbooks, and we contacted experts in the field of hepatobiliary surgery. It was included published and unpublished randomized controlled trials. It was evaluated the methodological quality of trials and, in duplicate, extracted data regarding operative, perioperative, and long-term outcomes. All authors were contacted and asked them to provide additional information regarding the trials. It was pooled results from the studies by using a random-effects model, evaluated the degree of heterogeneity, and explored potential explanations for heterogeneity. Six trials that included a total of 574 patients met eligibility criteria. In the pooled analysis, PPPD was 72 minutes faster (95 % confidence interval 53 to 92), with 284 mL less blood loss (95 % confidence interval 176 to 391) and 0.66 fewer units of blood transfused (95 % confidence interval 0.25 to 1.16). Other perioperative and long-term outcomes did not statistically differ, although the confidence intervals include important differences. It was concluded that moderate-quality evidence suggests PPPD is a faster procedure with less blood loss compared with SWPD. Large absolute differences in other key outcomes are unlikely;

excluding relatively small differences will, however, require larger, methodologically stronger trials [056].

Comparison of effectiveness between the pylorus-preserving pancreaticoduodenectomy "pylorus-preserving Whipple" and the classic Whipple procedure. A systematic literature search (Medline, Embase, Cochrane Library, Biosis, Science Citation Index, Ovid Journals) was performed to identify all eligible articles. Randomized controlled trials comparing pylorus-preserving pancreaticoduodenectomy versus classic Whipple for periampullary and pancreatic carcinoma were eligible for inclusion. The methodologic quality of included studies was evaluated independently by two authors. Quantitative data on perioperative parameters (blood loss, transfusion, operation time, and length of hospital stay), mortality, morbidity, and survival were extracted from included studies for meta-analysis. Pooled estimates of overall treatment effect were calculated using a random effects model. In total, 1235 abstracts were retrieved and checked for eligibility and six randomized controlled trials finally included. The critical appraisal revealed vast heterogeneity with respect to methodologic quality and outcome parameters. The comparison of overall in-hospital mortality (odds ratio 0.49; 95 % confidence interval 0.17 to 1.40), morbidity (odds ratio 0.89; 95 % confidence interval 0.48 to 1.62), and survival (hazard ratio, 0.74; 95 % confidence interval 0.52 to 1.07) showed no significant difference. However, operating time (weighted mean difference -68 minutes; 95 % confidence interval -106 to -31), and intraoperative blood loss (-766 mL; 95 % confidence interval -965 to -567) were significantly reduced in the pylorus-preserving group. Hence, in the absence of relevant differences in mortality, morbidity, and survival, the pylorus-preserving technique seems to be as effective as the classical Whipple. Given obvious clinical and methodological interstudy heterogeneity, efforts should be intensified in the future to perform high quality randomized trials of complex surgical interventions on the basis of well defined outcome parameters [057].

Several publications pointed out both advantages and disadvantages of both techniques and the current basis of evidence remains unclear. The objective of this systematic review is to compare the effectiveness of each technique. A search was conducted to identify all published and unpublished randomised controlled trials. Trials were identified by searching the following electronic databases - The Cochrane Library, MEDLINE, EMBASE and Current Contents. Reference lists from trials selected by electronic searching were hand-searched to identify further relevant trials. Randomised controlled trials comparing the classical Whipple with the pylorus-preserving pancreaticoduodenectomy were considered eligible if patients with periampullary or pancreatic carcinoma were included. Two authors independently extracted data for included studies. A random-effects model was used for pooling data from the different trials. Binary outcomes were compared using odds ratios, continuous outcomes were pooled using weighted mean differences and hazard ratios were used to for the meta-analysis of survival data. The methodological quality of included studies was evaluated independently by two authors according to quality standards and by using a questionnaire that covers different aspects of quality. 1235 abstracts were retrieved and checked for eligibility and seven randomized controlled trials were finally included. The critical appraisal revealed vast heterogeneity with respect to methodological quality and outcome parameters. The comparison of overall in-hospital mortality (odds ratio 0.49; 9 5% confidence interval 0.17 to 1.40), overall survival (hazard ratio 0.84; 95 % confidence interval 0.61 to 1.16) and morbidity showed no significant difference. However, operating time (weighted mean difference -68 min) and intra-operative blood loss (weighted mean difference -0.76 ml) were significantly reduced in the pylorus-preserving group. The authors concluded that there is no evidence of relevant differences in mortality, morbidity and survival between the pylorus-preserving pancreatoduodenectomy and the classical Whipple procedure. Given obvious clinical and methodological inter-study heterogeneity, future efforts have to be undertaken to perform high quality randomized controlled trials of complex surgical interventions on the basis of well defined outcome parameters [058].

Summary: The meta-analyses are also convicing – there are no important differences between the two methods.

Radically attempted surgery

Techniques of pancreaticojejunostomy

Leakage from pancreatic anastomoses remains the single most important morbidity after pancreaticoduodenectomy and contributes to prolonged hospitalization and mortality. The reported incidence after conventional pancreaticojejunostomy ranged from 10 percent to 29 percent. In a Chinese prospective, not-randomized study it was previously reported a new binding pancreaticojejunostomy technique with a leakage of 0 percent. A study now compared the postoperative pancreatic anastomosis leakage rate of a new binding technique with the conventional technique of pancreaticojejunostomy after pancreaticoduodenectomy in 217 patients who underwent pancreaticoduodenectomy for benign or malignant diseases of the pancreatic head and the periampullary region. Of the 111 patients randomized to the conventional group, pancreaticojejunostomy leakage occurred in 8 patients, while no patient in the 106 patients randomized to the binding group developed leakage (p=0.014). The overall postoperative complications developed in 41 patients (37 %) in the conventional group compared with 26 patients (25 %) in the binding group (p=0.048). Seven patients (6.3 %) died in the perioperative period in the conventional group compared with 3 patients (2.8 %) in the binding group, which was a not significant difference. The postoperative hospital stay (mean $\pm$ SD) for the conventional group was 22 $\pm$ 11 days, which was significantly longer than the binding group (18 $\pm$ 5 days). The authors concluded that binding pancreaticojejunostomy after panceaticoduodenectomy significantly decreased postoperative complication and pancreaticojejunostomy leakage rates and shortened hospital stay when compared with conventional pancreaticojejunostomy [059].

Comment: The results are convincing but must be read with some caution as the results come from the group that described the technique first. This means that it is not obvious that the same good results can be reached outside the group that is well familial with the technique. Also, the overall postoperative mortality is higher than what is usually reported from experienced center in the 2000s – the higher morbidity and mortality figures that are reported; the easier it is to improve! But … the binding anastomosis according to Peng is the most interesting news for a long time in pancreatic surgery.

To find out whether duct to mucosa anastomosis is better than classic "dunking" pancreaticojejunostomy a prospectively randomised study was performed. Ninty-three patients with periampullary cancer undergoing Whipple's operation were randomly divided into two groups. Forty-six with periampullary cancer underwent invaginating pancreaticojejunostomy, and 47 patients underwent duct to mucosa anastomosis for reconstruction. The over all mortality was 8 percent (7/93). An albumin concentration of less than 30 g/L before operation and operative blood loss influenced the surgical mortality both in the univariate and multivariate analysis. Age over 70 years was not a factor. Patients with duct to mucosa anastomoses had a leak rate of 4 percent (2/47), morbidity of 21 percent, and mortality of 6 percent. Patients with an invaginated pancreaticojejunostomy had a leak rate of 15 percent (7/46), morbidity of 33 percent, and mortality of 9 percent [060].

A modified technique
The majority of lethal complications after pancreatic head resection are due to septic complications after leakage from the pancreatojejunostomy. Especially the smooth pancreatic remnant is prone to develop parenchymal leaks from shear forces applied during tying of the sutures. It was developed a new mattress technique that avoids such shear

forces, and we compared this method to the standard Cattell (duct-to-mucosa) technique. A total of 113 patients undergoing standard pancreatic head resection were prospectively randomized to receive either the standard Cattell anastomosis (n=56) or the new mattress technique (n=57). All patients were evaluated for surgical and medical complications until discharge. Primary diagnosis and further demographic data compared well between the groups. The time to perform the mattress anastomosis was significantly shorter (15 vs 22 minutes). The incidence of complications at the pancreatojejunostomy, and the length of hospital stay and survival were not significantly different between the two groups; however, a trend toward more reoperations was noted in the Cattell group (10 vs 5). The new mattress technique is simple, and the data show that the two techniques yield similar incidences of complications [061].

Stenting of the anastomosis

Stent or no stent
Pancreatic fistula is a leading cause of morbidity and mortality after pancreatoduodenectomy. External drainage of pancreatic duct with a stent has been shown to reduce pancreatic fistula rate of pancreaticojejunostomy in a few retrospective or prospective nonrandomized studies, but no randomized controlled trial has been reported thus far. One single-center prospective randomized trial compared the results of pancreaticoduodenectomy with external drainage stent versus no stent for pancreaticojejunal anastomosis. A total of 120 patients undergoing pancreaticoduodenectomy with end-to-side pancreaticojejunal anastomosis were randomized to have either an external stent inserted across the anastomosis to drain the pancreatic duct (n=60) or no stent (n=60). Duct-to-mucosa anastomosis was performed in all cases. The two groups were comparable in demographic data, underlying pathologies, pancreatic consistency, and duct diameter. Stented group had a significantly lower pancreatic fistula rate compared with nonstented group (6.7 % vs 20 %). Radiologic or surgical intervention for pancreatic fistula was required in one patient in the stented group and four patients in the nonstented group. There were no significant differences in overall morbidity (31.7 % vs 38.3 %) and hospital mortality (1.7 % vs 5.0 %). Two patients in the nonstented group and none in the stented group died of pancreatic fistula. Hospital stay was significantly shorter in the stented group (mean 17 vs. 23 days). On multivariate analysis, no stenting and pancreatic duct diameter <3 mm were significant risk factors of pancreatic fistula. It was concluded that external drainage of pancreatic duct with a stent reduced leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy [062].

Internal stent or external stent
In pancreaticojejunostomy (PJ), the occurrence of an injury during the removal of a stented tube is sometimes related to pancreatitis or late-onset stenosis of the pancreatic duct. In one study, it was compared the outcomes of a PJ with an external stent versus an internal stent in a randomized study. It was compared the complications including pancreatic fistula, mortality, and postoperative hospital stay of 43 patients who had PJ with an external stent (group E) or PJ with an internal stent (group I) after a pancreaticoduodenectomy (PD). Pancreatic fistula occurred in 8 patients (36 %) in group E, while it only was seen in 7 patients (33 %) in group I. Pancreatitis was recognized in 3 patients in group E, while there was no patient in whom an obstruction due to an internal stent was suspected. It was concluded that pancreaticojejunostomy with an internal stent is therefore considered to be an effective treatment alternative after PD, with an acceptable morbidity and no mortality [063].

> Comment: There are enough studies to support the idea att a pancreatojejunostomy should be stented, but more studies are needed to know more of how and if only some patients could benefit of stents.

Pancreatogastrostomy versus pancreatojejunostomy

It was compared the results of pancreaticogastrostomy versus pancreaticojejunostomy following pancreaticoduodenectomy randomized in a total of 151 patients undergoing pancreaticoduodenectomy with soft residual tissue were randomized to receive either pancreaticogastrostomy (group PG) or end-to-side pancreaticojejunostomy (group PJ). The two treatment groups showed no differences in vital statistics or underlying disease, mean duration of surgery, and need for intraoperative blood transfusion. Overall, the incidence of surgical complications was 34 percent (29 % in PG, 39 % in PJ, which was a not significant difference). Patients receiving pancreatogastrostomy showed a significantly lower rate of multiple surgical complications. Pancreatic fistula was the most frequent complication, occurring in 15 percent of patients (13 % in PG and 16 % in PJ). Five patients in each treatment arm required a second surgical intervention; the postoperative mortality rate was 0.6 percent. Pancreatogastrostomy was favored over pancreatojejunostomy due to significant differences in postoperative collections, delayed gastric emptying, and biliary fistula. The mean postoperative hospitalization period stay was comparable in both groups [064].

Different methods of reconstruction after pancreaticoduodenectomy were used between January 1994 and January 1999 in two university-affiliated hospitals, pancreatojejunostomy, PJ, (n=69) in one hospital and pancreatogastrostomy, PG, (n=73) in the other. Operations at both hospitals were performed by the same surgical team. All pancreatic anastomoses were carried out in two layers with pancreatic duct stents. Pancreatic fistula was identified by the presence of more than 1000 units/l of amylase-rich fluid in the drains 7 days or more after operation, by radiography from the pancreatic duct stent and by water-soluble contrast upper gastrointestinal studies. The two groups of patients were similar in terms of age, gender, findings at preoperative assessment, disease status, operative time, intraoperative blood loss and nature of non-tumorous pancreatic tissue. The amylase level in ascites at 7 days after operation was significantly lower after PG than PJ. The incidence of pancreatic fistula in the PG group (zero) was significantly less than that after PJ (13 percent). Intra-abdominal hemorrhage and intra-abdominal abscess occurred in three (4 percent) and four patients (6 percent) respectively, with two hospital deaths (3 percent) in the PJ group, but these complications did not occur after PG. This controlled clinical study supports the hypothesis that pancreatogastrostomy is safer than pancreatojejunostomy, particularly with regard to the incidence of pancreatic fistula [065].

Only two large (more than 100 patients) prospective trials comparing pancreatogastrostomy (PG) with pancreatojejunostomy (PJ) after pancreatoduodenectomy (PD) have been reported until now. One nonrandomized study showed that there were less pancreatic and digestive tract fistulas with PG, whereas the other, a randomized trial from a single high-volume center, found no significant differences between the two techniques. A single blind, controlled randomized, multicenter trial was performed. The main endpoint was intra-abdominal complications. Of 149 randomized patients, 81 underwent PG and 68 PJ. No significant difference was found between the two groups concerning pre- or intraoperative patient characteristics. The rate of patients with one or more intra-abdominal complications was 34 percent in each group. Twenty-seven patients sustained a pancreatoenteric fistula (18 %), 13 in PG (16 %; 95 % confidence interval 8 to 24 %) and 14 in PJ (20 %; 95 % confidence interval 11 to 30 %). No statistically significant difference was found between the two groups concerning the mortality rate (11 % overall), the rate of reoperations and/or postoperative interventional radiology drainages (23 %), or the length of hospital stay (median 21 days). Univariate analysis found as risk factors age $\geq$ 70 years old, extrapancreatic disease, normal consistency of pancreas, diameter of main pancreatic duct <3 mm, duration of operation >6 hours, and a center effect. Significantly more intra-abdominal complications, pancreato-enteric fistula, and deaths occurred in one center (that included the most patients), but there were significantly more high-risk patients in this center (normal pancreas consistency, extrapancreatic pathology, small pancreatic duct, higher transfusion requirements, and duration of operation >6 hours) compared with the other centers. In multivariate analysis, the

center effect disappeared. Independent risk factors included duration of operation >6 hours for intra-abdominal complications and for pancreatoenteric fistula, extrapancreatic disease for pancreatoenteric fistulas, and age $\geq$ 70 years for mortality. It was concluded that the type of pancreatoenteric anastomosis (PJ or PG) after pancreatoduodenectomy does not significantly influence the rate of patients with one or more intra-abdominela infections and/or pancreatic fistula or the severity of complications [066].

> *Comment: Here are three well-performed randomized studies where the authors prefere pancreatogastrostomy to pancreatojejunostomy – results that has not been well acknowleged by the pancreatic surgeons. Is this because they are in doubt of the results, or is it because pancreatojejunostomy is more safe today than what was shown in the studies?*

A modified technique
Pancreatojejunostomy and pancreatogastrostomy (PG) are the commonly preferred methods of anastomosis after pancreatoduodenectomy (PD). Randomized controlled trials fails to show advantage of a particular technique, suggesting that both PJ and PG provide equally results. However, postoperative morbidity remains high. The best technique in pancreatic anastomosis is thus still debated. To compare the results of postoperative morbidity rate of a new pancreatogastrostomy technique, pylorus-preserving pancreaticoduodenectomy (PPPD) with gastric partition (PPPD-GP) with the conventional technique of pancreaticojejunostomy (PJ) a randomized trial was performed. Described was a new technique, PPPD-GP; in this technique the gastroepiploic arcade is preserved. Gastric partition was performed using 2 endo-Gia staplers along the greater curvature of the stomach, 3 cm from the border. This gastric segment, 10 to 12 cm in length is placed in close proximity to the cut edge of the pancreatic stump. An end-to-side, duct-to-mucosa anastomosis (with pancreatic duct stent) is constructed. One hundred eight patients undergoing PPPD for benign and malignant diseases of the pancreatic head and the periampullary region were randomized to receive PG (PPPD-GP) or end-to-side PJ (PPPD-PJ). The two treatment groups showed no differences in preoperative parameters and intraoperative factors. The overall postoperative complications were 23 percent after PPPD-GP and 44 percent after PPPD-PJ. The incidence of pancreatic fistula was 4 percent after PPPD-GP and 18 percent after PPPD-PJ. The mean hospital stay was 12 $\pm$ 2 days after PPPD-GP and 16 $\pm$ 3 days after PPPD-PJ. The authors concluded that the study showed that PPPD-GP can be performed safely and is associated with less complication than PPPD-PJ. The advantage of this technique over other PG techniques is that the anastomosis is outside the area of the stomach where the contents empty into the jejunum, but pancreatic juice drains directly into the stomach [067].

Meta-analyses
Pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) are the commonly preferred methods of anastomosis after pancreaticoduodenectomy (PD). The ideal choice of anastomosis remains a matter of debate. Articles published until end of March 2006 comparing PJ and PG after PD were searched. Two reviewers independently assessed quality and eligibility of the studies and extracted data for further analysis. Meta-analysis was performed with a random-effects model by using weighted odds ratios. Sixteen articles were included; meta-analysis of three randomized controlled trials revealed no significant difference between PJ and PG regarding overall postoperative complications, pancreatic fistula, intra-abdominal fluid collection, or mortality. On the contrary, analysis of 13 nonrandomized observational clinical studies showed significant results in favor of PG for the outcome parameters with a reduction of pancreatic fistula and mortality in favor of PG. It was thus found that all observational clinical studies reported superiority of PG over PJ, most likely influenced by publication bias. In contrast, all randomized trials failed to show advantage of a particular technique, suggesting that both pancreaticojejunostomy and pancreaticogastrostomy provide equally good results. This meta-analysis yet again highlights

the singular importance of performing well-designed randomized controlled trials and the role of evidence-based medicine in guiding modern surgical practice [068].

One paper compared rates of pancreatic fistula, morbidity and mortality after pancreaticoduodenectomy in patients having reconstruction by pancreaticogastrostomy with those in patients having reconstruction by pancreaticojejunostomy. A meta-analysis was performed of all large cohort and randomized controlled trials carried out since 1990. Eleven articles were identified for inclusion: one prospective randomized trial, two non-randomized prospective trials and eight observational cohort studies. The meta-analysis revealed a higher rate of pancreatic fistula associated with pancreaticojejunostomy reconstruction (relative risk 2.62; 95 % confidence interval 1.91 to 3.60). A higher overall morbidity rate was also demonstrated in this group (relative risk 1.43; 95 % confidence interval 1.26 to 1.61), as was a higher mortality rate (relative risk 2.51; 95 % confidence interval 1.61 to 3.91). It was concluded that the current literature suggests that the safer means of pancreatic reconstruction after pancreatoduodenectomy is pancreaticogastrostomy, but much of the evidence comes from observational cohort study data [069].

> Comment: If there is a difference between anastomosing the pancreatic remnant to the stomach or to jejunum there may be an advantage for pancreatogastrostomy. However, as the pancreatogastrostomy is new for most pancreatic surgeons there might be a publication bias in favor of the "new" technique. For most surgeons it is probably most important to be expert on one technique, but if scientific surgery is considered pancreatogastrostomy or the Peng binding technique most be born in mind.

Extended lymphadenectomy

It was compared operative morbidity, mortality, quality of life, and survival after pancreatoduodenectomy (PD) versus pancreatoduodenectomy with extended lymphadenectomy in patients with resectable pancreatic cancer. From 1997 to 2003 there were 132 patients with biopsy examination-proven or suspected adenocarcinoma of the pancreatic head who agreed to participate in a single-institution, prospective, randomized trial. If resectable at operation, patients then were randomized to standard PD (40 patients) or PD with extended lymphadenectomy (39 patients). Quality of life was assessed by using the Functional Assessment of Response to Cancer Therapy specific to the pancreas. Demographics and pathologic characteristics for both groups were similar. When comparing the extended procedure with standard PD, the median operating time was significantly greater for the extended group (7.6 h vs 6.2 h), blood transfusion more likely (44 % vs 22 %, p<0.05), and the median number of lymph nodes resected was significantly greater (36 vs 15 nodes). Morbidity and mortality rates were comparable. Median durations of stay were 11 and 11 days, respectively. There were no significant differences in 1-year (71 % vs 82 %), 3-year (25 % vs 41 %), 5-year (17 % vs 16 %), and median (19 vs 26 months) survival. At 4 months postoperatively, diarrhea, body appearance, and bowel control scored significantly lower on the Functional Assessment of Response to Cancer Therapy specific to the pancreas after the extended procedure. The authors concluded that although a much larger study would have more power to compare statistically the survival between groups, both the decrement in quality of life and similar studies showing no survival difference make extended lymphadenectomy together with pancreatoduodenectomy for pancreatic cancer unattractive for further prospective investigation [070].

In a prospective, randomized single-institution trial, the end points of a randomized study were to evaluate operative morbidity, operative mortality, and survival in patients undergoing standard versus radical (extended) pancreaticoduodenectomy. Between 1996 and 2001, 299 patients with periampullary adenocarcinoma were enrolled in a prospective, randomized

single-institution trial. After intraoperative verification (by frozen section) of margin-negative resected periampullary adenocarcinoma, patients were randomized to either a standard pancreaticoduodenectomy (removing only the peripancreatic lymph nodes en bloc with the specimen) or a radical (extended) pancreaticoduodenectomy (standard resection plus distal gastrectomy and retroperitoneal lymphadenectomy). All pathology specimens were reviewed, fully categorized, and staged. Of the 299 patients randomized, 5 (2 %) were subsequently excluded because their final pathology failed to reveal periampullary adenocarcinoma, leaving 294 patients for analysis (146 standard vs 148 radical). The two groups were statistically similar with regard to age (median 67 years) and gender (54 % male). All the patients in the radical group underwent distal gastric resection, while 86 percent of the patients in the standard group underwent pylorus preservation. The mean operative time in the radical group was 6.4 hours, compared to 5.9 hours in the standard group, which was a significant difference. There were no significant differences between the two groups with respect to intraoperative blood loss, transfusion requirements (median zero units), location of primary tumor (57 % pancreatic, 22 % ampullary, 17 % distal bile duct, and 3 % duodenal), mean tumor size (2.6 cm), positive lymph node status (74 %), or positive margin status on final permanent section (10 %). The mean total number of lymph nodes resected was significantly higher in the radical group. Of the 148 patients in the radical group, only 15 percent (n=22) had metastatic adenocarcinoma in the resected retroperitoneal lymph nodes, and none had retroperitoneal nodes as the only site of lymph node involvement. One patient in the radical group with negative pancreaticoduodenectomy specimen lymph nodes had a micrometastasis to one perigastric lymph node. There were six perioperative deaths (4 %) in the standard group versus three perioperative deaths (2 %) in the radical group, which was not significantly different. The overall complication rates were 29 percent for the standard group versus 43 percent for the radical group (a significant difference), with patients in the radical group having significantly higher rates of early delayed gastric emptying and pancreatic fistula and a significantly longer mean postoperative stay. With a mean patient follow-up of 24 months, there were no significant differences in 1-, 3-, or 5-year and median survival when comparing the standard and radical groups. The authors concluded that radical (extended) pancreaticoduodenectomy can be performed with similar mortality but some increased morbidity compared to standard pancreaticoduodenectomy. The data failed to indicate that a survival benefit is derived from the addition of a distal gastrectomy and retroperitoneal lymphadenectomy to a pylorus-preserving pancreaticoduodenectomy [071].

The usefulness of performing an extended lymphadenectomy and retroperitoneal soft-tissue clearance in conjunction with a pancreatoduodenal resection in the treatment of ductal adenocarcinoma of the head of the pancreas is still unknown. Published studies suggest a benefit for the procedure in terms of better long-term survival rates; however, these studies were retrospective or did not prospectively evaluate large series of patients. Therefore a study was conducted to determine whether the performance of an extended lymphadenectomy and retroperitoneal soft-tissue clearance in association with a pancreatoduodenal resection improves the long-term survival of patients with a potentially curable adenocarcinoma of the head of the pancreas. Eighty-one patients undergoing a pancreatoduodenal resection for a potentially curable ductal adenocarcinoma of the head of the pancreas were randomized to a standard (n=40) or extended (n=41) lymphadenectomy and retroperitoneal soft-tissue clearance in a prospective, multicentric study. The standard lymphadenectomy included removal of the anterior and posterior pancreatoduodenal, pyloric, and biliary duct, superior and inferior pancreatic head, and body lymph node stations. In addition to the above, the extended lymphadenectomy included removal of lymph nodes from the hepatic hilum and along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to both renal hila, with circumferential clearance of the origin of the celiac trunk and superior mesenteric artery. Patients did not receive any postoperative adjuvant therapy. Demographic (age, gender) and histopathologic (tumor size, stage, differentiation, oncologic clearance) characteristics were similar in the two patient groups. Performance of the extended lymphadenectomy added time to the procedure, although the difference did not

reach statistical significance (397 ± 50 minutes vs 372 ± 50 minutes). Transfusion requirements, postoperative morbidity and mortality rates, and overall survival did not differ between the two groups. When subgroups of patients were analyzed, using an a posteriori analysis that was not planned at the time of study design, there was a significantly longer survival rate in node positive patients after an extended rather than a standard lymphadenectomy. The survival curve of node positive patients after an extended lymphadenectomy could be superimposed onto the curves of node negative patients. Survival curves in node negative patients did not differ according to the magnitude of the lymphadenectomy. Multivariate analysis of all patients showed that long-term survival was significantly affected by tumor differentiation (well vs moderately vs poorly differentiated), diameter ≤ 2.0 cm vs > 2.0 cm), lymph node metastasis (absent vs present) and need for 4 or more units of transfused blood (< 4 vs ≥ 4). The authors concluded that the addition of an extended lymphadenectomy and retroperitoneal soft-tissue clearance to a pancreatoduodenal resection does not significantly increase morbidity and mortality rates. The survival rate does not differ in the two groups [072].

> *Summary: The three studies show that extended lymphadenectomy is of no benefit to the patients after a pancreatic cancer resection. There is no need for further studies on this, unless some new factor appears, e.g. an effective adjuvant treatment to those with positive lymph nodes.*

Meta-analysis
To compare outcomes between pancreaticoduodenectomy (PD) and extended pancreaticoduodenectomy (EPD) from all published comparative studies in the literature using meta-analytical techniques a study compared operative details, post-operative adverse events and survival following PD and EPD. Comparative studies published between 1988 and 2005 of PD versus EPD were included. End points were classified into peri-operative details, post-operative complications including 30-day mortality, and survival as measured during follow up. A random effect model was employed. Sixteen comparative studies comprising 1909 patients (865 PD and 1044 EPD), including 3 randomized controlled trials with 454 patients (226 PD and 228 EPD) were identified. Tumour size was comparable between the groups. Significantly more lymph nodes were harvested from those patients undergoing EPD (a median of 14 more nodes, but it is not known if the techniques were comparable). Operative time was significantly longer in EPD (49 min) and there was a trend towards fewer positive resection margins (odds ratio 1.78). Peri-operative adverse events were similar between the groups with only delayed gastric emptying (odds ratio 0.59) occurring significantly less frequently in the PD group. Peri-operative mortality (odds ratio 1.48) and long-term survival (hazard ratio 0.77) showed a non-significant trend favouring EPD. Extended pancreatoduodenectomy is associated with a greater nodal harvest and fewer positive resection margins than pancreatoduodenectomy. However, the risk of delayed gastric emptying is increased and no significant survival benefit has been shown [073].

Ligation of the pancreatic remnant duct

Anastomotic leak of the pancreaticojejunostomy is a major cause of morbidity and mortality following pancreaticoduodenectomy. Reports have described a large variety of techniques for performing this anastomosis and managing the pancreatic stump. In an attempt to obviate the pancreaticojejunostomy, it was prospectively studied the technique of ligating the pancreatic duct and using external drains to create a temporary controlled pancreaticocutaneous fistula. Thirty-five consecutive patients who were to undergo pancreaticoduodenectomy for periampullary carcinoma were prospectively randomized to one of two groups: pancreaticojejunostomy (PJ) (n=18) or controlled pancreaticocutaneous fistula (CPF) (n = 17). The groups were well matched for age, gender, coexisting medical illnesses, type of tumor, and preoperative condition. Except for the management of the

pancreatic remnant, all patients in both groups underwent an identical procedure. Major morbidity, length of hospitalization, duration of the controlled pancreatic fistula, and mortality were analyzed over a mean follow-up interval of 26 months (range 5 months to 8 years). The CPF group experienced significantly lower overall operative morbidity rates than the PJ group (24 % vs 56 %). Two patients (11 %) in the PJ group and none in the CPF group died. Half the morbidity in the PJ group and both mortalities were related to anastomotic leak. The CPF and PJ groups left the hospital after mean stays of 26 and 42 days, respectively, which was a significant difference. Compared to pancreaticojejunal anastomosis, creation of a temporary controlled pancreaticocutaneous fistula in patients who undergo pancreato-duodenectomy for periampullary malignancy has no appreciable risk. It was in this study associated with reduced morbidity and shorter length of hospitalization [074].

> *Comment: This method is today (2010) outdated, not least due to the high risk of postoperative diabetes rather soon after the operation. Also, the postoperative length of stay in hospital in the studies is conciderably longer than is usual.*

Gluing the remnant to decrease the risk of pancreatic fistula

Postoperative complications after pancreaticoduodenectomy are largely due to leakage of the pancreaticoenterostomy. Pancreatic duct occlusion without anastomosis of the pancreatic remnant may prevent these complications. Therefore, a prospective randomized study to assess morbidity and pancreatic function after pancreaticoduodenectomy with pancreaticojejunostomy and duct occlusion without pancreaticojejunostomy was performed in a nonselected series of 169 patients with suspected pancreatic and periampullary cancer. In 86 patients the pancreatic duct was occluded without anastomosis to pancreatic remnant, and in 83 patients a pancreaticojejunostomy was performed after pancreaticoduodenectomy. Postoperative complications were the endpoint of the study. Patient characteristics were comparable in both groups. There were no differences in median blood loss, duration of operation, and hospital stay. No significant difference was noted in postoperative complications, mortality, and exocrine insufficiency. The incidence of diabetes mellitus was significantly higher in patients with duct occlusion. This means that duct occlusion without pancreaticojejunostomy does not reduce postoperative complications but significantly increases the risk of endocrine pancreatic insufficiency after duct occlusion [075].

Of three nonrandomized studies, two reported no fistulas after intracanal injection and ductal occlusion with fibrin glue after pancreatoduodenectomy with immediate pancreatodigestive anastomosis, while another study reported no protective effect of glue injection. To determine whether temporary occlusion of the main pancreatic duct with human fibrin glue decreases the incidence of intra-abdominal complications after pancreatoduodenectomy or distal pancreatectomy (DP) a prospective, randomized, single-blinded, multicenter study, conducted between 1995 and 1999, included 182 consecutive patients undergoing pancreatoduodenectomy followed by immediate pancreatic anastomosis or DP, whether for benign or malignant tumor or for chronic pancreatitis. One hundred two underwent pancreatic resection followed by ductal occlusion with fibrin glue (made slowly resorbable by the addition of aprotinin); 80 underwent resection without ductal occlusion. The main end point was the number of patients with one or more of the following intra-abdominal complications: pancreatic or other digestive tract fistula, intra-abdominal collections (infected or not), acute pancreatitis, or intra-abdominal or digestive tract hemorrhage. Severity factors included postoperative mortality, repeat operations, and length of hospital stay. The two groups were similar in pre- and intraoperative characteristics except that there were significantly more patients in the ductal occlusion group who were receiving octreotide, who had reinforcement of their anastomosis by fibrin glue, and who had fibrotic pancreatic stumps. However, the rate of patients with one or more intra-abdominal complications, and notably with pancreatic fistula, did not differ significantly between the two groups. There was still no significant

difference found after statistical adjustment for these patient characteristic discrepancies, confirming the inefficacy of fibrin glue. The rate of intra-abdominal complications was significantly higher in the presence of a normal, nonfibrotic pancreatic stump and main pancreatic duct diameter less than 3 mm, whereas reinforcement of the anastomosis with fibrin glue or use of octreotide did not influence outcome. In multivariate analysis, however, normal pancreatic parenchyma was the only independent risk factor for intra-abdominal complications. No significant differences were found in the severity of complications between the two groups. The authors concluded that ductal occlusion by intracanal injection of fibrin glue decreases neither the rate nor the severity of intra-abdominal complications after pancreatic resection [076].

It was performed a prospective randomized study including 97 patients (34 F, 63 M). Forty six were affected by pancreatic inflammatory diseases and 51 had pancreatic or peripancreatic neoplasms. All the patients were managed by the same surgical staff. Surgical treatment included 30 pancreaticoduodenectomies, 40 pancreatico-jejunostomies, 23 left pancreatic resections and 4 tumour excisions. The patients were randomized at the moment the surgical treatment was chosen and divided into 2 different groups: group A, including 43 subjects who had intraoperative fibrin sealing, and group B, including 54 patients who had no fibrin sealing during surgery. At the end of the trial, 6 patients in group A (14 %) and 6 in group B (11 %) developed a pancreatic fistula. No statistically significant difference was detected between the 2 groups. The highest incidence of fistulas was observed in the patients with pancreatic cancer in group A (19 %) [077].

> *Summary: Three randomized studies show that gluing of the pancreatic remnant's duct is of no benefit.*

Postoperative drains

The use of surgically placed intraperitoneal drains has been considered routine after pancreatic resection. Recent studies have suggested that for other major upper abdominal resections, routine postoperative drainage is not required and may be associated with an increased complication rate. After informed consent, eligible patients with peripancreatic tumors therefore were randomized during surgery either to have no drains placed or to have closed suction drainage placed in a standardized fashion after pancreatic resection. One hundred seventy-nine patients were enrolled in the study, 90 women and 89 men. Mean age was 65 years (range 23-87). The pancreas was the tumor site in 142 (79 %) patients, with the ampulla (n=24), duodenum (n=10), and distal common bile duct (n=3) accounting for the remainder. A pancreaticoduodenectomy was performed in 139 patients and a distal pancreatectomy in 40 cases. Eighty-eight patients were randomized to have drains placed. Demographic, surgical, and pathologic details were similar between both groups. The overall 30-day death rate was 2 percent (n=4). A postoperative complication occurred during the initial admission in 107 patients (59 %). There was no significant difference in the number or type of complications between groups. In the drained group, 11 patients (13 %) developed a pancreatic fistula. Patients with a drain were more likely to develop a significant intraabdominal abscess, collection, or fistula. The authors concluded that the randomized prospective clinical trial failed to show a reduction in the number of deaths or complications with the addition of surgical intraperitoneal closed suction drainage after pancreatic resection. The data suggest that the presence of drains failed to reduce either the need for interventional radiologic drainage or surgical exploration for intraabdominal sepsis [078].

> *Comment: This is a very important RCT – there are not even indications that draining the abdominal cavity after routine pancreatic resection is needed. Omitt the drains!*

Delayed postoperative hemorrhage

It was investigated whether interventional radiology or laparotomy is the best management of delayed postoperative hemorrhage (DPH) after pancreaticoduodenectomy by an electronic search of MEDLINE and selected for analysis only original articles published between 1990, and 2007. Two investigators independently selected studies reporting on clinical presentation and incidence of postoperative DPH and the following outcomes: complete hemostasis, morbidity, and mortality. A random-effects meta-analytical technique was used for analysis. One hundred sixty-three cases of DPH after pancreaticoduodenectomy were identified from the literature. The incidence of DPH after pancreaticoduodenectomy was 3.9 percent. Seventy-seven patients (47 %) underwent laparotomy; 73 (45 %) interventional radiology and 13 (8 %), conservative treatment. On meta-analysis there were no significant difference found between the two treatment options for complete hemostasis (73 % vs 76 %), mortality (43 % vs 20 %), or morbidity (77 % vs 35 %). It was concluded that this meta-analysis, although based on data from small case series, is unable to demonstrate any significant difference between laparotomy and interventional radiology in the management of DPH after pancreaticoduodenectomy. The management of this life-threatening complication is difficult, and the appropriate treatment pathway ultimately will be decided by the clinical status of the patient and the institution preference [079].

> *Comment: This is a very inhomogenous group of patients and it is difficult to randomize the patients. Moreover, the techniques of interventional radiology is developing fast, which make it even more difficult to perform valuable and sustainable field in this field.*

Palliative surgery

Surgery versus stenting in laparoscopically unresectable cancer

Laparoscopy and laparoscopic ultrasound were performed in 297 consecutive patients with peripancreatic carcinoma scheduled for surgery after radiologic staging. Patients with pathology-proven unresectable tumors were randomly allocated to either surgical or endoscopic palliation. All others underwent laparotomy. Laparoscopic staging detected biopsy-proven unresectable disease in 39 patients (13 %). At laparotomy, unresectable disease was found in another 72 patients, leading to a detection rate for laparoscopic staging of 35 percent. In total, 145 of the 197 patients classified as having "possibly resectable" disease after laparoscopic staging underwent resection (74 %). Average survival in the group of 14 patients with biopsy-proven unresectable tumors randomly allocated to endoscopic palliation was 116 days, with a mean hospital-free survival of 94 days. The corresponding figures were 192 days and 164 days in the 13 patients allocated to surgical palliation. The authors concluded that because of the limited detection rate for unresectable metastatic disease and the likely absence of a large gain after switching from surgical to endoscopic palliation, laparoscopic staging should not be performed routinely in patients with peripancreatic carcinoma [080].

Meta-analysis
The objective of one analysis was to compare endoscopic stenting with surgical bypass in patients with unresectable, malignant, distal common bile duct obstruction using the technique of meta-analysis. The inclusion criteria for the studies were randomized patient assignment, publication in the English language, 20 or more patients per group, all patients followed up until death, and follow-up and complications reported in an equivalent way for

both treatment arms. Data extraction was performed independently by two of the authors. The number of treatment failures, serious complications, requirement for additional treatment sessions, and 30-day mortality were extracted. Three existing trials met the inclusion criteria, all of which compared surgery with the use of plastic stents. There were no studies identified that used metallic expandable stents. For the rate of treatment failure and serious complications, the odds ratios of the 3 trials were heterogeneous, and no summary odds ratio were calculated. More treatment sessions were required after stent placement than after surgery, and a common odds ratio was estimated to be 7.23 (95 % confidence interval 3.73 to 13.98). Thirty-day mortality was not significantly different (odds ratio 0.52; 95 % confidence interval 0.26 to 1.04). Although surgical bypass required fewer additional treatment sessions, existing data do not allow a definitive conclusion on which treatment is preferable [081].

> Comment: The surgeons have already "voted" in this question – endoscopic stenting is today the first choice in patients not otherwise needing laparotomy. To re-change this routine there must be very strong advantages for open surgery, and so far there is not.

Radical surgery versus by-pas

To evaluate, the early and long-term results of mono-bloc spleno-pancreatic and vascular resection for advanced carcinoma of the head of the pancreas, with portal-mesenteric venous invasion 56 patients with advanced carcinoma of the head of the pancreas with vascular invasion were studied. Patients were randomly divided an en-bloc spleno-pancreatic and vascular resection or a palliative gastro-biliary bypass. Patients in both groups were subjected to adjuvant locoregional chemoimmunotherapy, through an arterial catheter introduced into the superior mesenteric artery via a jejunal arterial branch. The 2- and 5-year survival rates for the resected patients were 82 percent and 19 percent. The respective percentages for disease-free survival were 61 percent and 0 percent. Two-year survival for the not resected was nil [082].

Retrocolic or antecolic gastroenterostomy?

The pathogenesis of delayed gastric emptying (DGE) after pylorus-preserving pancreato-duodenectomy (PPPD) has been speculated to be related to factors such as inflammation, ischemia, gastric atony, motilin levels, and type of surgical procedure. Previous retrospective studies have shown a lower incidence of DGE after antecolic duodenojejunostomy. Forty patients were enrolled in this trial between 2002 and 2004. Just before duodenojejunostomy during PPPD, the patients were randomly assigned to undergo either an antecolic or a retrocolic duodenojejunostomy. DGE occurred in 5 percent of patients with the antecolic route for duodenojejunostomy versus 50 percent with the retrocolic route. Those with the antecolic route had a significantly shorter duration of postoperative nasogastric tube drainage than did those with the retrocolic route (4 days versus 19 days, respectively). By postoperative day 14, all patients with the antecolic route could take solid foods, while only 55 percent (11 of 20) of the patients with the retrocolic route could take solid foods. The length of stay in the hospital was 28 days for the antecolic group versus 48 days for the retrocolic group. Antecolic reconstruction for duodenojejunostomy during PPPD decreases postoperative morbidity and length of hospital stay by decreasing delayed gastric emptying. The data suggest that pylorus-preserving pancreatoduodenectomy with antecolic duodenojejunostomy is a safer operation [083].

> Comment: All stomach/duodenal-enteric anastomoses should be antecolic.

Ante- or isoperistaltic gastrojejunostomy?

To compare two different types of prophylactic gastric bypass in patients with cancer of the pancreatic head who were not suitable for curative resection a prospective study 44 patients with unresectable cancer of the pancreatic head without duodenal obstruction who presented between 1995 and 2000 who were randomised into 2 groups. Twenty-two patients had an antecolic, isoperistaltic gastrojejunostomy, jejunojejunostomy, and hepaticojejunostomy after cholecystectomy. The remaining 22 had a hepaticojejunostomy and antecolic, antiperistaltic gastrojejunostomy procedure after cholecystectomy. There were no significant differences between the groups in the incidence of postoperative complications, time until restoration of oral diet, relaparotomy rate, late upper gastrointestinal bleeding, mortality, duration of hospital stay, and survival. The isoperistaltic operation took significantly longer than the antiperistaltic operation and there was less delayed gastric emptying in the antiperistaltic group but not significantly so. Both operations caused a significant lengthening in the postoperative gastric emptying time [084].

Prophylactic gastrojejunostomy at laparotomy?

Between 25 and 75 percent of patients with periampullary cancer who undergo exploratory surgery with intent to perform a pancreaticoduodenectomy are found to have unresectable disease. Most will undergo a biliary-enteric bypass. Whether or not to perform a prophylactic gastrojejunostomy remains unresolved. Retrospective reviews of surgical series and prospective randomized trials of endoscopic palliation have demonstrated that late gastric outlet obstruction, requiring a gastrojejunostomy, develops in 10-20 percent of patients with unresectable periampullary cancer. Therefore, a prospective, randomized, single-institution trial was designed to evaluate the role of prophylactic gastrojejunostomy in patients found at exploratory laparotomy to have unresectable periampullary carcinoma. Between 1994 and 1998, 194 patients with a periampullary malignancy underwent exploratory surgery with the purpose of performing a pancreaticoduodenectomy and were found to have unresectable disease. On the basis of preoperative symptoms, radiologic studies, or surgical findings, the surgeon determined that gastric outlet obstruction was a significant risk in 107 and performed a gastrojejunostomy. The remaining 87 patients were thought by the surgeon not to be at significant risk for duodenal obstruction and were randomized to receive either a prophylactic retrocolic gastrojejunostomy or no gastrojejunostomy. Short- and long-term outcomes were determined in all patients. Of the 87 patients randomized, 44 patients underwent a retrocolic gastrojejunostomy and 43 did not undergo a gastric bypass. The two groups were similar with respect to age, gender, procedure performed (excluding gastrojejunostomy), and surgical findings. There were no postoperative deaths in either group, and the postoperative morbidity rates were comparable (gastrojejunostomy 32 %, no gastrojejunostomy 33 %). The postoperative length of stay was 8.5 $\pm$ 0.5 days for the gastrojejunostomy group and 8.0 $\pm$ 0.5 days for the no gastrojejunostomy group. Mean survival among those who received a prophylactic gastrojejunostomy was 8 months, and during that interval gastric outlet obstruction developed in none of the 44 patients. Mean survival among those who did not have a prophylactic gastrojejunostomy was 8 months. In 8 of those 43 patients (19 %), late gastric outlet obstruction developed, requiring therapeutic intervention (gastrojejunostomy 7 patients, endoscopic duodenal stent 1 patient), which is a statistically significant difference. The median time between initial exploration and therapeutic intervention was 2 months. The results from this prospective, randomized trial demonstrate that prophylactic gastrojejunostomy significantly decreases the incidence of late gastric outlet obstruction. The performance of a prophylactic retrocolic gastrojejunostomy at the initial surgical procedure does not increase the incidence of postoperative complications or extend the length of stay. According to the authors a retrocolic gastrojejunostomy should therefore be performed routinely when a patient is undergoing surgical palliation for unresectable periampullary carcinoma [085].

The value of prophylactic gastroenterostomy (usually combined with a biliary bypass) in patients with unresectable cancer of the pancreatic head was systematically reviewed regarding retrospective and prospective studies, and a meta-analysis of prospective studies, on the use of prophylactic gastroenterostomy for unresectable pancreatic cancer were performed. Analysis of retrospective studies did not reveal any advantage or disadvantage of prophylactic gastroenterostomy. Three prospective studies comparing prophylactic gastroenterostomy plus biliodigestive anastomosis with no bypass or a biliodigestive anastomosis alone were identified (altogether 218 patients). For patients who had prophylactic gastroenterostomy, the chance of gastric outlet obstruction during follow-up was significantly lower (odds ratio 0.06; 95 percent confidence interval 0.02 to 0.21). The rates of postoperative delayed gastric emptying were similar in both groups (OR 1.93; 95 percent confidence interval 0.57 to 6.53), as were morbidity and mortality. The estimated duration of hospital stay after prophylactic gastroenterostomy was 3 days longer than for patients without bypass (weighted mean difference 3.1; 95 percent confidence interval 0.7 to 5.5), which was a statistically significant difference. It was concluded that a prophylactic gastroenterostomy should be performed during surgical exploration of patients with unresectable pancreatic head tumours because it reduces the incidence of long-term gastroduodenal obstruction without impairing short-term outcome [086].

Several studies, including one randomized trial, propagate to perform a prophylactic gastrojejunostomy routinely in patients with periampullary cancer found to be unresectable during laparotomy. Others suggest an increase of postoperative complications. Controversy still exists in general surgical practice if a double bypass should be performed routinely in these patients. To evaluate the effect of a prophylactic gastrojejunostomy on the development of gastric outlet obstruction and quality of life in patients with unresectable periampullary cancer found during explorative laparotomy. Between 1998 and 2002, patients with a periampullary carcinoma who were found to be unresectable during exploration were randomized to receive a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy). Randomization was stratified for center and presence of metastases. Patients with gastrointestinal obstruction and patients treated endoscopically for more than 3 months were excluded. Primary endpoints were development of clinical gastric outlet obstruction and surgical intervention for gastric outlet obstruction. Secondary endpoints were mortality, morbidity, hospital stay, survival, and quality of life, measured prospectively by the EORTC-C30 and Pan26 questionnaires. It was decided to perform an interim analysis after inclusion of 50 percent of the patients (n=70). Five of the 70 patients randomized were lost to follow-up. From the remaining 65 patients, 36 patients underwent a double and 29 a single bypass. There were no differences in patient demographics, preoperative symptoms, and surgical findings between the groups. Clinical symptoms of gastric outlet obstruction were found in 2 of the 36 patients (6 %) with a double bypass, and in 12 of the 29 patients (41 %) with a single bypass. In the double bypass group, one patient (3 %) and in the single bypass group 6 patients (21 %) required (re)gastrojejuno-stomy during follow-up, which was a significant difference. The absolute risk reduction for reoperation in the double bypass group was 18 percent, and the numbers needed to treat was 6. Postoperative morbidity rates, including delayed gastric emptying, were 31 percent in the double versus 28 percent in the single bypass group. Median postoperative length of stay was 11 days (range 4-76 days) in the double versus 9 days (range 6-20 days) in the single bypass group; median survival was 7 months in the double versus 8 months in the single bypass group. No differences were found in the quality of life between both groups. After surgery most quality of life scores deteriorated temporarily and were restored to their baseline score within 4 months. It was concluded that prophylactic gastrojejunostomy significantly decreases the incidence of gastric outlet obstruction without increasing complication rates. There were no differences in quality of life between the two groups. Together with the previous randomized trial from the Johns Hopkins group, this study provides sufficient evidence to state that a double bypass consisting of a hepaticojejuno-stomy and a prophylactic gastrojejunostomy is preferable to a single bypass consisting of

only a hepaticojejunostomy in patients undergoing surgical palliation for unresectable periampullary carcinoma. Therefore, the trial was stopped earlier than planned [087].

Summary: All the three available studies advocates a prophylactic gastrojejunostomy if the patient for some reason has a laparotomy and irresectable pancreatic cancer.

Bilio-enteric anastomosis

Twenty patients treated by cholecystojejunostomy for obstructive icterus were randomized to be treated either with a biofragmentable intraluminal ring (Valtrac) (10 patients) or suture of the cholecystointestinal anastomosis (10 patients). Postoperatively one patient in each group died of advanced malignancy. There were no surgical complications in either group. The relief of icterus, recovery of the gastrointestinal tract and the mean hospital stay were similar in both groups. The authors concluded that biofragmentable anastomosis ring is a safe method for cholecystoenteral anastomoses [088].

A prospective, randomized clinical trial was conducted to assess the efficacy of bilioenteric bypass in noncalculous distal biliary obstruction. Thirty-one patients required bypass for either malignant obstruction or chronic pancreatitis and were randomized into two groups: cholecystoenterostomy or choledochoenterostomy with cholecystectomy. Nine bypasses failed after cholecystoenterostomy and two after choledochoenterostomy, which was a significant difference. Eight of the 9 failures occurred in the subgroup of 22 patients with malignant biliary obstruction. In this subgroup, five bypasses failed within 90 days of operation, all after cholecystoenterostomy, which was a significant difference. The results indicate that choledochoenterostomy is the superior operation for malignant distal biliary obstruction [089].

Ultrasonic dissection

Resection of the non-fibrotic pancreas is prone to postoperative pancreatic fistula because of well preserved exocrine secretions and easily crushed soft parenchyma. The purpose of this study was to evaluate ultrasonic dissection for division of the non-fibrotic pancreas in distal pancreatectomy. All pancreata included in this study were soft on direct palpation and their main ducts had no dilatation, at least proximally from the transection line. Fifty-eight patients with gastric cancer or pancreatic disease were randomly assigned to the two groups. In the ultrasonic dissection group (n=27), all pancreatic ducts were identified and ligated securely. The stump was left open without parenchymal suturing. In the conventional group (n=31), the pancreas was cut with a knife and the stump was oversewn in mattress fashion. The main pancreatic duct was ligated in all patients in both groups. Pancreatic fistula was defined as a pancreatic fluid discharge for more than 7 days after operation diagnosed according to amylase concentration in the drainage fluid. In the ultrasonic dissection group, approximately 20-30 tubes including a mean 5.2 ± 0.8 (range 4-6) pancreatic ducts were skeletonized and ligated per patient. There were nine pancreatic fistulas (16 %); one in the ultrasonic dissection group and eight in the control group. It was concluded that in distal pancreatectomy for the non-fibrotic pancreas, ultrasonic dissection without suture closure of the stump reduced the incidence of pancreatic fistula compared with conventional division and suture, in this randomized trial [090].

Surgery versus chemotherapy

The advantage of resection over radiochemotherapy has not yet been confirmed by a randomized trial. It was therefore conducted a study to compare surgical resection alone versus radiochemotherapy without resection for locally invasive pancreatic cancer using a multicenter randomized design. Patients with pancreatic cancer who met our preoperative criteria for inclusion (pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric artery or the common hepatic artery, or without distant metastasis) underwent laparotomy. Patients with operative findings consistent with the criteria were randomized into a radical resection group and a radiochemotherapy group (200 mg/m^2/day of intravenous 5-fluorouracil and 5040 cGy of radiotherapy) without resection. The two groups were compared for mean survival, hazard ratio, 1-year survival, quality of life scores, and hematologic and blood chemical data. Twenty patients were assigned to the resection group and 22 to the radiochemotherapy group. There was 1 operative death. The surgical resection group had significant better results than the radiochemotherapy group as measured by 1-year survival (62 % vs 32 %), mean survival time (>17 vs 11 months), and hazard ratio (0.46). There were no differences in the quality of life score or laboratory data apart from increased diarrhea after surgical resection. This means that locally invasive pancreatic cancer without distant metastases and major arterial invasion appears to be best treated by surgical resection [091, 092].

Octreotide and somatostatin

The aim of one study was to evaluate the influence of low dose perioperative octreotide on the prevention of complications (pancreatic fistula and general complications) in patients undergoing pancreatic surgery followed by pancreatico-jejunostomy. 105 patients were randomized to receive either octreotide 0.1 mg subcutaneously 3 times/day for a total of 7 days or no octreotide. The primary endpoints were the occurrence of a pancreatic fistula and/or general complications including the length of hospital stay. There were 25 surgical draining procedures performed and 80 duodeno-pancreatectomies with or without preservation of the pylorus. Twenty-six (25 %) of the patients were treated for chronic pancreatitis, 8 (8 %) for benign tumoral disease and 71 (68 %) for carcinoma. All patients underwent pancreatico-jejunostomy. Fifty-six patients received octreotide and 49 did not. The incidence of fistula formation in the octreotide group was 9 percent (n=5) and in the control group 8 percent (n=4) for a total incidence of 9 percent. The difference between the two groups was not statistically significant. There was one death in the octreotide group and none in the control group for an overall mortality of 0.9 percent. The morbidity, except fistulas, was 11 percent in the octreotide group and 12 percent in the control group. The length of hospital stay was 23 $\pm$ 15 days in the group receiving octreotide vs 20 $\pm$ 8 days in the control group (a not significant difference). Stratifying the data for duodenopancreatectomy and for draining procedures there was no difference between the groups either. The authors concluded that in patients undergoing pancreatic surgery and pancreatico-jejunostomy, the perioperative use of 3 x 0.1 mg octreotide for 7 days does not reduce general complications nor fistula formation [093].

A prospective, randomized controlled clinical trial was conducted in 33 Italian surgical departments with the aim of evaluating the efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections. Between 1990 and 1992, 278 patients were enrolled in the study. Fifty-four dropped out because of unresectable disease and six were excluded because of protocol violation; the remaining 218 were randomly assigned to the octreotide group (n=111) or to the placebo group (n=107). There were 131 men and 87 women with a mean age of 58 years. Pancreaticoduodenectomy was the most common operation performed (n=143), sixty-four percent of patients had a pancreatic or periampullary cancer; chronic pancreatitis accounted for 8 percent of cases. Mortality rate was 6.9 percent. A pancreatic fistula occurred in 31 patients (14 %), 9 percent in the octreotide group and 20 percent in the placebo group, which was a significant difference. Morbidity rate was

significantly lower in the octreotide (22 %) than in the placebo group (36 %), which also was a significant difference. When specific pancreatic complications were grouped together and evaluated, they occurred significantly less frequently in the treated (15 %) than in the placebo group (30 %) [094].

An Italian prospective multicentre study evaluated the efficacy of octreotide, a synthetic somatostatin analogue, in preventing the complications of elective pancreatic surgery. 303 patients with tumours of the pancreas or the ampullary region, in whom ultrasonography and computed tomography scan had shown a resectable lesion, or with chronic pancreatitis, were randomized in a double-blind fashion to treatment with octreotide 100 micrograms t.i.d. s.c. starting at least 1 h before surgery and continued till the 7th postsurgical day, or with matching placebo. Unresectable lesions were found at laparatomy in 31 patients (15 % of those with tumours). In 14 others, procedures not anticipated in the study protocol had to be performed, and in 6 additional cases there were other protocol violations so that these 20 patients were excluded from the study analysis. Considering the 252 evaluable patients, the complication rate was significantly higher in the 130 placebo-treated patients than in the 122 who received octreotide (29 % vs 16 %) [095].

In a randomized placebo-controlled German multicentric and double-blind trial it was analyzed the role of octreotide in the prevention of post-operative complications after major pancreatic surgery. A significant reduction of complications (fistula, abscess, fluid collection, sepsis, pulmonary insufficiency, postoperative acute pancreatitis) could be demonstrated in patients receiving octreotide (3 x 100 micrograms/day s.c.). The effect of octreotide was particularly true in patients undergoing a Whipple resection for cancer [096].

In a prospective trial 30 patients underwent pancreaticoduodenectomy (Whipple operation) for cancer. They were randomly assigned to receive somatostatin (n=15) or not (n=15). Somatostatin was started at laparotomy with 250 micrograms/h and given over a period of 5 days. A small catheter, which was placed into the duct of the pancreatic remnant, gave access to the pancreatic juice. Volume, amylase, lipase and protein as well as bicarbonate outputs were analyzed. As regards endocrine function, insulin and glucagon plasma levels were measured. The nitrogen balance was calculated. A stimulation test was done on the fifth postoperative day. Six patients (3/3) were assessed as drop-outs. A significant reduction was found for volume, amylase, lipase, protein and bicarbonate with somatostatin, this effect lasting for two days. Lipase however was reduced significantly for 5 days. Pancreatic exocrine function was reduced as well after stimulation, if somatostatin was given. Insulin and glucagon were inhibited with somatostatin, the latter more effectively. It was found a positive nitrogen-balance as early as on the second postoperative day in the somatostatin-group, whereas without somatostatine this did not occur before the fourth postoperative day. These findings were significant on the third and fourth postoperative day [097].

A prospective, randomized, controlled trial was performed to determine the efficacy of somatostatin in the prevention of pancreatic stump-related complications with elimination of surgeon-related factors in high-risk patients undergoing pancreaticoduodenectomy. From 1997 to 2000, 54 patients with age ranged from 32 to 89 years, were randomly assigned to somatostatin group (n=27) or placebo group (n=27). Ninety-four percent of the patients had pancreatic and periampullary lesions; 6 percent had secondary lesion involving the duodenum such as local recurrent colon carcinoma and renal cell carcinoma. These patients received either standard pancreaticoduodenectomy or pylorus-preserving pancreatico-duodenectomy. An experienced surgeon performed all operations in same fashion to minimize the surgical factor. A transanastomotic tube was inserted into the pancreatic duct for diversion of pancreatic juice in the pancreaticojejunostomy for a 3-weeks period postoperatively. Intravenous infusion of somatostatin was given at a dose of 250 microg/hr in the somastotatin group and normal saline was given to the control group for 7 days

postoperatively. There was one perioperative death in each group, resulting in a 3.7% mortality rate. In the somastotatin group, as compared to the placebo group, the incidence of overall morbidity and pancreatic stump related complications were significantly lower with a mean decrease of 50 percent pancreatic juice output and a slightly shorter duration of hospital stays. In conclusion, after excluding surgeon related factor, prophylactic use of somatostatin reduces the incidence and severity of pancreatic stump related complications in high-risk patients having pancreaticoduodenectomy via decreased secretion of pancreatic exocrine [098].

In yet another study the effects of somatostatin-14 (S-14) on pancreatic remnant exocrine secretion were assesses in a double-blind, randomized, placebo-controlled trial in patients undergoing pancreaticoduodenectomy for malignancy. Patients received a continuous infusion of S-14 (n=38) or placebo (n=37) for 7 days. Pancreatic juice and peripancreatic drainage fluid was collected and measured, and pancreatic enzymes were monitored daily. S-14 infusion was associated with a decrease in median daily pancreatic juice and pancreatic amylase output. Amylase concentration and output in the peripancreatic drain fluid were significantly lower after S-14 infusion than in the control group. The incidence of clinical pancreatic fistula (two of 38 vs eight of 37) and total pancreatic stump-related complications (five of 38 vs 12 of 37) were lower in patients treated with S-14. Duration of hospital stay was significantly shorter after S-14 (18 vs 26 days) [099].

The aim in one study was to determine if vapreotide, a potent long-acting somatostatin analogue, would decrease pancreas-related complications. This prospective, multicenter, randomized, double-blind, placebo-controlled trial involved 275 patients without preexisting chronic pancreatitis undergoing elective proximal, central, or distal pancreatectomy. Complications were defined by objective criteria before beginning the study. One hundred thirty-five patients received vapreotide; 140 patients received placebo. There were no statistically significant differences between vapreotide- and placebo-treated patients in either pancreas-related complications (30 % vs 26 %) or in other complications not directly related to the pancreas (40 % vs 42 %). The author concluded that the somatostatin analogue vapreotide does not appear to decrease postoperative complications after major pancreatectomy in patients without chronic pancreatitis [100].

Prophylactic administration of octreotide acetate decreases the rate of postoperative intra-abdominal complications after elective pancreatic resection. In a single-blind, controlled, randomized multicenter (n=20) trial in France 230 randomized patients undergoing pancreatoduodenectomy and pancreatic enteric anastomosis or distal pancreatectomy for either malignant or benign tumor or chronic pancreatitis, 122 were allotted intraoperatively to receive octreotide; 108 served as controls. All 230 patients were analyzed. Both groups were comparable except that significantly more patients in the octreotide group had biological glue injected into the main pancreatic duct alone or reinforcing the pancreatic enteric anastomosis (68 % vs 39 %). Fewer patients in the octreotide group sustained one or more intra-abdominal complications (22 % vs 32 %). In subgroup analysis, octreotide significantly reduced the rate of patients sustaining one or more intra-abdominal complication when the main pancreatic duct diameter was less than 3 mm, when pancreatojejunostomy was performed, or both. No significant differences were found regarding complication severity. Twenty-three patients (10 %) died postoperatively, 16 (70 % of deaths) of whom had one or more intra-abdominal complications. The only independent risk factor for complications found on multivariate analysis was pancreatoduodenectomy compared with distal pancreatectomy (odds ratio 3.54; 95 % confidence interval 1.44 to 8.65). The results suggest that octreotide is not necessary for all patients undergoing pancreatic resection; it could be useful when the main pancreatic duct is less than 3 mm in diameter and when pancreatoduodenectomy is completed by pancreatojejunostomy [101].

Four randomized, placebo-controlled, multicenter trials from Europe evaluated prophylactic octreotide (the long-acting synthetic analog of native somatostatin) in patients undergoing pancreatic resection. Each trial reported significant decreases in overall complication rates, and two of the four reported significantly lowered rates of pancreatic fistula in patients receiving prophylactic octreotide. However, none of these four trials studied only pancreaticoduodenal resections, and all trials had high pancreatic fistula rates (>19 %) in the placebo group. A fifth randomized trial from the United States evaluated the use of prophylactic octreotide in patients undergoing pancreaticoduodenectomy and found no benefit to the use of octreotide. Prophylactic use of octreotide adds more than USD 75 to the daily hospital charge in the United States. In calendar year 1996, 288 patients received octreotide on the surgical service at the authors' institution, for total billed charges of USD 74,652. To evaluate the endpoints of complications (specifically pancreatic fistula and total complications) and death in patients undergoing pancreaticoduodenectomy 383 patients were recruited into one study between 1998 and 2000 on the basis of preoperative anticipation of pancreaticoduodenal resection. Patients who gave consent were randomized to saline control versus octreotide 250 microg subcutaneously every 8 hours for 7 days, to start 1 to 2 hours before surgery. The primary postoperative endpoints were pancreatic fistula, total complications, death, and length of hospital stay. Two hundred eleven patients underwent pancreaticoduodenectomy with pancreatic-enteric anastomosis, received appropriate saline/octreotide doses, and were available for endpoint analysis. The two groups were comparable with respect to demographics (54 % male, median age 66 years), type of pancreaticoduodenal resection (60 % pylorus-preserving), type of pancreatic-enteric anastomosis (87 % end-to-side pancreaticojejunostomy), and pathologic diagnosis. The pancreatic fistula rates were 9 percent in the control group and 11 percent in the octreotide group. The overall complication rates were 34 percent in the control group and 40 percent in the octreotide group; the in-hospital death rates were 0 percent versus 1 percent, respectively. The median postoperative length of hospital stay was 9 days in both groups. These data demonstrate that the prophylactic use of perioperative octreotide does not reduce the incidence of pancreatic fistula or total complications after pancreatoduoden-ectomy. Prophylactic octreotide use in this setting should be eliminated, at a considerable cost savings [102].

Summary: The picture is not totally clear even though there now is a substantial number (at least 10) of studies on somatostatin's and somatostatin analogue's role as prophylaxis against postoperative complications after pancreatic resections. There are doubtless more studies showing a benefit for octreotide et al than not, but the latest published did not find any benefit for this rather expensive drug. From a theoretical point of view it may be argued that the less perfect the surgery is, the more likely it is to find an effect of octreotide – and by time there are indications that the surgery is getting better …

Somatostatin
One study assessed the effects of somatostatin-14 (S-14) on pancreatic remnant exocrine secretion. It was a double-blind, randomized, placebo-controlled trial in patients undergoing pancreaticoduodenectomy for malignancy. Patients received a continuous infusion of S-14 (n=38) or placebo (n=37) for 7 days. Pancreatic juice and peripancreatic drainage fluid was collected and measured, and pancreatic enzymes were monitored daily. Postoperative complications were recorded. S-14 infusion was associated with a decrease in median daily pancreatic juice and pancreatic amylase output. Amylase concentration and output in the peripancreatic drain fluid were significantly lower after S-14 infusion than in the control group. The incidence of clinical pancreatic fistula (two of 38 versus eight of 37) and total pancreatic stump-related complications (five of 38 versus 12 of 37) was significantly lower in patients treated with S-14. Duration of hospital stay was significantly shorter after S-14 (18 versus 26 days). Although the effect of S-14 on exocrine secretion remains difficult to demonstrate, it did reduce pancreatic juice leakage from the pancreatic remnant [103].

Effect on gastric emptying

Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) are common complications after pancreaticoduodenectomy. Whereas several prospective randomized trials propose the prophylactic use of octreotide to prevent pancreatic fistula formation, somatostatin has, however, been associated with delayed gastric emptying after partial duodenopancreatectomy. In one prospective, randomized, double-blinded, placebo-controlled trial it was analyzed the influence of prophylactic octreotide on delayed gastric empting after pancreaticoduodenectomy. Patients were randomized to the placebo group (n=32) and the octreotide group (n=35). Primary endpoint was the incidence of delayed gastric emptying, secondary endpoints included perioperative morbidity other than DGE. DGE was measured by clinical signs, gastric scintigraphy and the hydrogen breath test. Risk factors for DGE other than octreotide were analyzed by univariate and multivariate analyses. DGE measured by clinical signs was similar between both groups studied (approximately 20 % of the patients). Gastric scintigraphy (T½) was 76 $\pm$ 15 min in the octreotide group and 87 $\pm$ 18 min in controls at day 7, respectively. The H_2 breath test was 65 $\pm$ 7 min in octreotide treatment group and 67 $\pm$ 6 min in controls at day 8. POPF grade C occurred in approximately 3 percent of the patients, although prophylactic treatment of octreotide did not reduce the incidence of POPF. Multivariate analysis showed that postoperative intraabdominal bleeding and infection were independent risk factors for DGE. Furthermore preoperative biliary stenting reduced postoperative DGE after partial duodenopancreat-ectomy. It was concluded that prophylactic octreotide has no influence on gastric emptying and does not decrease the incidence of postoperative pancreatic fistula after pancreaticoduodenectomy [104].

> *Comment: It is important to know that octreotide does not cause delayed gastric emptying*

Meta-analyses

Pancreatic fistula is one of the most common complications after elective pancreatic surgery. Several clinical trials have evaluated the use of octreotide to prevent the development of pancreatic fistula after pancreatic surgery with conflicting recommendations. To assess the effectiveness of octreotide in preventing postoperative pancreatic fistula it was undertaken a meta-analysis of 7 identified randomized controlled trials, reporting comparisons between octreotide and a control. The primary outcome was the incidence of postoperative pancreatic fistula, and the secondary outcome was the postoperative mortality. Seven studies, involving 1359 patients, met the inclusion criteria for this review. In these studies, sample sizes ranged from 75 to 252 patients. In total, 679 patients were given octreotide and 680 patients formed the control group. Perioperative octreotide is associated with a significant reduction in the incidence of pancreatic fistula after elective pancreatic surgery, with a relative risk of 0.59 (95 % confidence interval 0.41 to 0.85). However, this risk reduction was not associated with a significant difference in postoperative mortality. The review revealed that perioperative octreotide is associated with a significant reduction in the incidence of pancreatic fistula after elective pancreatic surgery. However, this risk reduction was not associated with a significant difference in postoperative mortality [105].

A literature search using Medline and ISI Proceedings with exploration of the references identified 22 studies on role of somatostatin and its analogues in reducing complications after pancreatic resection. Of these, ten met the inclusion criteria for data extraction. Estimates of effectiveness were performed using fixed- and random-effects models. Outcomes for 1918 patients were compared. Somatostatin and its analogues did not reduce the mortality rate after pancreatic surgery (odds ratio 1.17; 95 % confidence interval 0.70 to 1.94) but did reduce both the total morbidity (odds ratio 0.62; 95 % confidence interval 0.46 to 0.85) and

pancreas-specific complications (odds ratio 0.56; 95 % confidence interval 0.39 to 0.81). Somatostatin and its analogues reduced the rate of biochemical fistula (odds ratio 0.45; 95 % confidence interval 0.33 to 0.62) but not the incidence of clinical anastomotic disruption (odds ratio 0.80; 95 % confidence interval 0.44 to 1.45) [106].

The aim of one study was to evaluate, through systematic review, the effectiveness of somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of established enterocutaneous pancreatic fistulas. Electronic databases, including Medline and EMBASE, were searched systematically by using keywords including "somatostatin", "octreotide", "fistula" and "randomiz(s)ed controlled trial". In addition, citations of relevant primary and review articles were examined. Particular authors were contacted when necessary. Data on patient recruitment, intervention and outcome were extracted from the included trials and analysed. Use of somatostatin or octreotide for the prevention of postpancreatectomy complications, including pancreatic fistulas, was identified in 14 randomized controlled trials, including one abstract and one conference proceeding, involving a total of 1686 patients. Use of somatostatin or octreotide for the treatment of established enterocutaneous pancreatic fistulas was identified in ten trials involving a total of 301 patients. Significant heterogeneity was found among the identified trials with regard to the definition of fistula, dosage of octreotide, starting time and duration of the treatment, among other factors. There was major disagreement between the studies on whether use of the drugs in question is of value in preventing postoperative complications. This analysis suggests that, in units where the postoperative fistula rate following pancreatoduodenectomy for neoplasia and other pancreatic conditions exceeds 10 percent, somatostatin or octreotide administered before operation may significantly reduce the rate of major postoperative complications, particularly pancreatic fistulas. The identified evidence also suggests that there may be a limited role for such drugs in the treatment of established postoperative enterocutaneous pancreatic fistulas [107].

Summary: It may now be concluded that if the rate of pancreatoenteric leak following pancreatic cancer resections exceeds one in ten (or something like that) somatostatin or octreotide is cost-effective, even though the drugs probably do not affect mortality. The figures point towards a selective use of octreotide in soft pancreatic remnants.

Anaesthesiological techniques

In the last years the criteria of operability have been extended to elderly patients with hepato-pancreatic-biliary diseases. It was selected 46 patients (in the seventies or older, class 3 or 4 of ASA score, affected by hepato-pancreatic-biliary neoplasms) in order to evaluate the behavior of these patients undergoing to different anaesthesiological techniques. Randomly, it was treated 24 patients (group A) in general anaesthesia, and 22 patients (group B) in peridural anaesthesia. Mortality rate was similar in the two groups (A = 4.1 %, B = 4.5 %), and no complications were determined by the different anesthesiologic procedures. Pleuritis was present in 44 percent of group A versus 45 percent of group B. Atelectasis areas were present in 58 percent of group A versus 27 percent of group B, pneumonia was present in 33 percent of group A versus 9 percent of group B, which was a significant difference. There were no differences between the two groups regarding wound infection rate (only one case in group B) [108].

Systemic rather than surgical complications cause the majority of perioperative deaths, so the anesthesiologist has a crucial role in the management of these patients. It was sought to evaluate an improved approach to perioperative pain management, postsurgical complications as well as outcomes. From 2002 to 2007, 40 patients underwent pancreaticoduodenectomy for pancreatic or periampullary cancer. The anesthesia protocol was standardized for postoperative pain control. Patients were randomly divided into two

groups: 16 patients received an epidural analgesia with local anesthetics combined with opioids (T_9-T_{10}; group A) and 24 had intravenous analgesia with morphine (group B). Postoperative mortality was 2.5 percent. With regard to complications we observed 4 biliary fistulas, 2 pancreatic fistulas with spontaneous healing in one patient and death in the other as well as wound infections. Patients treated with epidural analgesia experienced better pain relief, compared with subjects receiving intravenous analgesia, which demonstrated a higher incidence of opioid-related adverse effects such as sedation and respiratory depression. It was concluded that adequate perioperative treatment included suitable nutritional support and pain management using loco-regional techniques, which seem to improve the surgical outcomes among pancreatic cancer patients [109].

Blood sugar monitoring

To evaluate a closed-loop system providing continuous monitoring and strict control of perioperative blood glucose following pancreatic resection a prospective, randomized clinical trial with 30 patients were prospectively randomized. Perioperative blood glucose levels were continuously monitored using an artificial endocrine pancreas (STG-22). Glucose levels were controlled using either the sliding scale method (sliding scale group, n=13) or the artificial pancreas (artificial pancreas group, n=17). The incidence of severe hypoglycemia (<40 mg/dL) during the intensive care period following pancreatic resection in patients was monitored with the artificial pancreas. The secondary outcome measure was the total amount of insulin required for glycemic control in the first 18 hours after pancreatic resection in each patient group. In the sliding scale group, postoperative blood glucose levels rose initially before reaching a plateau of approximately 200 mg/dL between 4 and 6 hours after pancreatectomy. The levels remained high for 18 hours postoperatively. In the artificial pancreas group, blood glucose levels reduced steadily, reaching the target zone (80-110 mg/dL) by 6 hours after surgery. The total insulin dose administered per patient during the first postoperative 18 hours was significantly higher in the artificial pancreas group (mean, 107 IU) than the sliding scale group (8 IU). Neither group showed hypoglycemia. It was concluded that perioperative use of an artificial endocrine pancreas to control pancreatogenic diabetes after pancreatic resection is an easy and effective way to maintain near-normal blood glucose levels. The artificial pancreas shows promise for use as insulin treatment for patients with pancreatogenic diabetes after pancreatic resection [110].

Postoperative administration of albumin

Surgeons commonly see postoperative hypoalbuminemia, but whether exogenous albumin administration is beneficial for these patients is unclear. A prospective, randomized study design was used, allocating 127 hypoalbuminemic patients into the albumin or saline group after gastrointestinal surgery. It was investigated the development of postoperative hypoalbuminemia, nutritional status, postoperative fluid balance, postoperative complications, and postoperative hospital stay. Plasma albumin concentrations of both groups decreased significantly after operations. No significant differences were found between groups in changes in postoperative plasma albumin concentration from baseline levels. Postoperative plasma albumin, total protein, and prealbumin levels were similar in the two groups. While 3-day and 5-day recovery ratios were similar, 7-day recovery ratios were lower in the albumin group. No significant difference was found in overall fluid administration, urine output, or the incidence of postoperative complications between groups (23 % for albumin group and 13 % for control group). It was concluded that albumin administration in the early stage of postoperative hypoalbuminemia following gastrointestinal surgery is not beneficial in correcting hypoalbuminemia or in clinical outcomes [111].

Summary: albumin administration in the early stage of postoperative hypoalbuminemia

following gastrointestinal surgery is not beneficial.

Postpancreatectomy fistula rate

Pancreatic fistula (PF) is one of the most common complications after pancreato-duodenectomy. There have been no large prospective randomized trials evaluating PF rates comparing invagination versus duct to mucosa pancreaticojejunostomy. Between 2006 and 2008, 197 patients at two institutions underwent pancreaticoduodenectomy by a total of 8 experienced pancreatic surgeons as part of this prospective randomized trial. All patients were stratified by pancreatic texture and randomized to either an invagination or a duct to mucosa pancreaticojejunal anastomosis. Recorded variables included pancreatic duct diameter, operative time, blood loss, complications, and pathology. Primary end point was PF rate, as defined by the International Study Group on Pancreatic Fistula. Secondary end points included PF grade, postoperative length of hospital stay, other morbidities, and mortality. Rate of PF for the entire cohort was 18 percent. There were 23 fistulas (24 %) in the duct to mucosa cohort and 12 fistulas (12 %) in the invagination cohort. The greatest risk factor for a PF was pancreas texture: PF developed in only 8 patients (8 %) with hard glands, and in 27 patients (27 %) with a soft gland. There were two perioperative deaths (both in the duct to mucosa group), with the proximate causes of death being PF, followed by bleeding and sepsis. This dual-institution prospective randomized trial revealed considerably fewer fistulas with invagination compared with duct to mucosa pancreaticojejunostomy after pancreaticoduodenectomy. Results confirm increased pancreatic fistula rates in soft as compared with hard glands [112].

Postpancreatectomy nutritional support

Many clinical studies have demonstrated that early postoperative enteral nutrition (EN) improved the postroperative course. Post-pancreaticoduodenectomy patients tend to suffer from postoperative nausea, abdominal distention, and diarrhoea, causing difficulty in the introduction of EN. In one pilot study, it was investigated the appropriate nutritional mode post-pancreatic surgery. Between 2006 and 2007 two postoperative nutritional methods were implemented in 17 patients in a prospective single-centere study. Eight patients received only enteral nutrition (EN group) and 9 patients received enteral nutrition combined with parenteral nutrition (EN + PN group). There were no differences in the patient characteristics and postoperative morbidity between the two groups. The rate of discontinuance of enteral feeding was significantly high in the EN group, and the duration of enteral feeding was significantly longer in the EN + PN group. The central venous line was retained for a significantly longer period in the EN + PN group, but there was no difference in the frequency of catheter-related infection between the 2 groups. The authors concluded that enteral nutrition combined with parenteral nutrition is most adequate for patients after pancreatic surgery [113].

Psychotherapeutic postoperative support

The impact of psychotherapeutic support on survival time in patients with gastrointestinal cancer undergoing surgery was studied. A randomized controlled trial was conducted in cooperation with the Departments of General Surgery and Medical Psychology, University Hospital of Hamburg, Germany. Two hundred and seventy-one consenting patients with a preliminary diagnosis of cancer of the esophagus, stomach, liver/gallbladder, pancreas or colon/rectum were stratified by gender and randomly assigned to a control group that received standard care, as provided on the surgical wards, or to an experimental group that

received formal psychotherapeutic support in addition to routine care during the hospital stay. Patients in both groups completed the EORTC-Quality of Life questionnaire pre-operatively, post-operatively, and at 3, 6, 12, and 24 months following surgery. Date of death, if applicable, was also recorded. Unadjusted and adjusted survival analyses were performed. Kaplan-Meier survival curves demonstrated significantly better survival for the experimental group than for the control group up to 2 years. Cox regression models that took TNM Staging or the Residual Tumor Classification into account also found significant differences at the 2-year follow-up. Secondary analyses found that most of the differences in favor of the experimental group occurred in females and in patients with stomach, pancreatic, primary liver or colorectal cancer. The results of this study indicate that patients with gastrointestinal cancer, particularly those who are female and those who undergo surgery for stomach, pancreatic, primary liver or colorectal cancer, benefit from a formal program of psychotherapeutic support in terms of survival [114].

Quality of life

One study was undertaken to determine the effect of home healthcare on the quality of life (QOL) in patients diagnosed with gastrointestinal cancer. A total of 42 patients, who met eligibility criteria, were enrolled in the study and randomly assigned to either a control group or an experimental group. Control group patients received "usual care" defined as pain control and management through the pain clinic. Experimental group patients received pain control through the clinic plus three home visits. During the home visits, their nursing care was guided by an evidence-based protocol developed by the research team. Data were collected on pain, performance, symptoms, and QOL by using previously developed and validated instruments.Significant differences were found between the two groups on physiological function, psychological concerns, and total stress. In the experimental group, there was a significant decrease in pain and increase in performance from baseline to the final data collection period. For the control group, a significant decrease in QOL over the study period was observed. There were no significant differences between the two groups on pain, performance, QOL, and QOL subscales at the final visit [115].

Low-molecular heparin prophylaxis

Clinical trials are needed to assess the clinical benefit of antithrombotic prophylaxis in patients with cancer who are receiving chemotherapy, since these patients are at an increased risk of developing a thromboembolism. It was performed a trial to assess the clinical benefit of the low-molecular-weight heparin nadroparin for the prophylaxis of thromboembolic events in ambulatory patients receiving chemotherapy for metastatic or locally advanced solid cancer. Between 2003, and 2007, ambulatory patients with lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer were randomly assigned in a double-blind manner to receive subcutaneous injections of nadroparin (3800 IU anti-Xa once a day, n=779) or placebo (n=387), in a 2:1 ratio. Study treatment was given for the duration of chemotherapy up to a maximum of 4 months. The primary study outcome was the composite of symptomatic venous or arterial thromboembolic events, as assessed by an independent adjudication committee. All randomised patients who received at least one dose of study treatment were included in the efficacy and safety analyses (modified intention-to-treat population). 1150 patients were included in the primary efficacy and safety analyses: 769 patients in the nadroparin group and 381 patients in the placebo group. 15 (2.0 %) of 769 patients treated with nadroparin and 15 (3.9 %) of 381 patients treated with placebo had a thromboembolic event, which was a significant difference Five (0.7 %) of 769 patients in the nadroparin group and no patients in the placebo group had a major bleeding event. The incidences of minor bleeding were 7.4 percent (57 of 769) with nadroparin and 7.9 percent (30 of 381) with placebo. There were 121 (15.7%) serious adverse events in the nadroparin

goup and 67 (17.6 %) serious adverse events in the placebo group. Nadroparin reduces the incidence of thromboembolic events in ambulatory patients with metastatic or locally advanced cancer who are receiving chemotherapy. Future studies should focus on patients who are at a high risk for thromboembolic events [116].

CHEMOTHERAPY

Surgery versus chemotherapy

The preliminary results of a multi-institutional randomized controlled trial revealed better survival after surgery than after radiochemotherapy. It was now reported the final results of this study after 5 years of follow-up. Patients with preoperative findings of pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric or common hepatic arteries, or distant metastasis, were included in this randomized controlled trial, with their consent. If the laparotomy findings were consistent with these criteria, the patient was randomized to a surgery group or a radiochemotherapy group (5-fluorouracil 200 mg/m^2/day and 5040 Gy radiotherapy). The surgery and radiochemotherapy groups comprised 20 and 22 patients, respectively. Patients were followed up for 5 years or longer, or until an event occurred to preclude this. The surgery group had significantly better survival than the radiochemotherapy group. Surgery increased the survival time and 3-year survival rate by an average of 12 months and 20 percent, respectively, and it halved the instantaneous mortality (hazard) rate. It was concluded that locally invasive pancreatic cancer without distant metastases or major arterial invasion is treated most effectively by surgical resection [117].

> Comment: This is a small but well designed study, which confirme the empirically reached knowledge by most surgeons. As long as the morbidity and the mortality rates are kept low and the patients are radically operated it is probably not even ethically right to perform more randomized studies on this issue.

Adjuvant treatment

ESPAC

The European Study Group for Pancreatic Cancer (ESPAC) assessed the roles of chemoradiotherapy and chemotherapy in a randomised study. After resection, patients were randomly assigned to adjuvant chemoradiotherapy (20 Gy in ten daily fractions over 2 weeks with 500 mg/m^2 fluorouracil intravenously on days 1-3, repeated after 2 weeks) or chemotherapy (intravenous fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 days, monthly for 6 months). Clinicians could randomise patients into a two-by-two factorial design (observation, chemoradiotherapy alone, chemotherapy alone, or both) or into one of the main treatment comparisons (chemoradiotherapy versus no chemoradiotherapy or chemotherapy versus no chemotherapy). The primary endpoint was death, and all analyses were by intention to treat. 541 eligible patients with pancreatic ductal adenocarcinoma were randomised: 285 in the two-by-two factorial design (70 chemoradiotherapy, 74 chemotherapy, 72 both, 69 observation); a further 68 patients were randomly assigned chemoradiotherapy or no chemoradiotherapy and 188 chemotherapy or no chemotherapy. Median follow-up of the 227 (42 %) patients still alive was 10 months (range 0-62). Overall results showed no benefit for adjuvant chemoradiotherapy (median survival 16 months in 175 patients with chemoradiotherapy vs 16 months in 178 patients without; hazard ratio 1.2; 95 % CI 0.9 to 1.6). There was evidence of a significant survival benefit for adjuvant chemotherapy (median survival 20 months in 238 patients with chemotherapy vs 14 months in 235 patients without; hazard ratio 0.66; 95 % CI 0.52-0.83). The authors concluded that the study showed no survival benefit for adjuvant chemoradiotherapy but revealed a potential benefit for adjuvant chemotherapy [118].

It was also assessed the influence of resection margins on survival for patients with resected pancreatic cancer treated within the context of the ESPAC-1 study as it is known that patients with positive microscopic resection margins (R1) have a worse survival, but it is not

known how they fare in adjuvant studies. ESPAC-1 set out to look at the roles of chemoradiation and chemotherapy. Randomization was stratified prospectively by resection margin status. Of 541 patients with a median follow-up of 10 months, 101 (19 %) had R1 resections. Resection margin status was confirmed as an influential prognostic factor, with a median survival of 11 months for R1 versus 17 months months for patients with R0 margins. Resection margin status remained an independent factor in a Cox proportional hazards model only in the absence of tumor grade and nodal status. There was a survival benefit for chemotherapy but not chemoradiation, irrespective of R0/R1 status. The median survival was 20 months with chemotherapy versus 14 months without. For patients with R0 margins, chemotherapy produced longer survival compared with to no chemotherapy. This difference was less apparent for the smaller subgroup of R1 patients, but there was no significant heterogeneity between the R0 and R1 groups. This means that the resection margin-positive pancreatic tumors represent a biologically more aggressive cancer; these patients benefit from resection and adjuvant chemotherapy but not chemoradiation. The magnitude of benefit for chemotherapy treatment is reduced for patients with R1 margins versus those with R0 margins [119].

The five-year results of the European Study Group for Pancreatic Cancer 1 Trial were then presented in 2004. In a multicenter trial using a two-by-two factorial design, it was randomly assigned 73 patients with resected pancreatic ductal adenocarcinoma to treatment with chemoradiotherapy alone (20 Gy over a two-week period plus fluorouracil), 75 patients to chemotherapy alone (fluorouracil), 72 patients to both chemoradiotherapy and chemotherapy, and 69 patients to observation. The analysis was based on 237 deaths among the 289 patients (82 percent) and a median follow-up of 47 months (interquartile range, 33 to 62). The estimated five-year survival rate was 10 percent among patients assigned to receive chemoradiotherapy and 20 percent among patients who did not receive chemoradiotherapy, which was a significant difference. The five-year survival rate was 21 percent among patients who received chemotherapy and 8 percent among patients who did not receive chemotherapy, which was also statistically significant. The benefit of chemotherapy persisted after adjustment for major prognostic factors. The author concluded that adjuvant chemotherapy has a significant survival benefit in patients with resected pancreatic cancer, whereas adjuvant chemoradiotherapy has a deleterious effect on survival [120].

Cox proportional hazard modelling was used to also investigate the influence of type of surgery and the presence of complications on survival in conjunction with clinico-pathological variables in the 550 patients of the ESPAC-1 adjuvant randomized controlled trial. Standard Kausch-Whipple (KW) was performed in 282 (54 %) patients, 186 (35 %) had a pylorus-preserving (PP) KW, 39 (7 %) had a distal pancreatectomy and 21 (4 %) had a total pancreatectomy. Post-operative complications were reported in 140 (27 %) patients. PP-KW patients survived significantly longer with a median (95 % CI) survival of 20 (17, 23) months compared to 15 (13, 17) for KW patients. The difference might at least in part be explained by KW patients being significantly more likely to have R1 margins (24 % vs 16 %), poorly differentiated tumours (26 % vs 10 %) and positive lymph nodes (60 % vs 44 %). Post-operative complications did not significantly affect survival. Independent prognostic factors were tumour grade, nodal status and tumour size but not type of surgery or post-operative complications. There was a survival benefit for chemotherapy irrespective of the type of surgery or post-operative complications. The authors concluded that the type of surgery procedures did not significantly influence the hazard of death in the presence of tumour staging. Post-operative complications did not adversely affect the survival benefit from adjuvant chemotherapy [121].

The ESPAC-1, ESPAC-1 plus, and early ESPAC-3(v1) results (458 randomized patients; 364 deaths) were used to estimate the effectiveness of adjuvant 5FU/FA vs resection alone for pancreatic cancer using meta-analysis. The pooled hazard ratio of 0.70 (95 % confidence

interval 0.55 to 0.88) was statistically significant, and the median survival of 23 (95 % confidence interval 20 to 27) months with 5FU/FA versus 17 (95 % confidence interval 14 to 19) months with resection alone supports the use of adjuvant 5FU/FA in pancreatic cancer [122].

Comment: It is interesting to note that there was a positive correlation between having an R0 operation and longer survival, but also between having an R1 operation and positive lymph nodes. In this material there are no hints that a pylorus-preserving procedure should be less oncologic radical – rather the opposit. On the other hand, the randomization was between adjuvant chemotherapy or not, which means that the surgeons may have selected patients to a pyloruspreserving procedure due to causes not measured or recorded.

Summary: ESPAC has shown several things:
- *it is possible to gather as many patients as needed, and follow them up for a long time, for adjuvant studies even when large number is needed for enough statistical power*
- *it is possible to get European (and others as well) surgeons to work together for a good goal*
- *it is possible to get surgeons and oncologists to work together for a good goal*
- *adjuvant therapy is of benefit for patients operated with radical intent for exocrine pancreatic cancer*
- *adjuvant radiotherapy is of no benefit (potentially harmful) together with the cytostatics used for patients operated with radical intent for exocrine pancreatic cancer*

Gemcitabine

One multicentre randomised phase III trial was designed to determine whether adjuvant chemotherapy with gemcitabine improves the outcomes of patients with resected pancreatic cancer. Eligibility criteria included macroscopically curative resection of invasive ductal carcinoma of the pancreas and no earlier radiation or chemotherapy. Patients were randomly assigned at a 1 to 1 ratio to either the gemcitabine group or the surgery-only group. Patients assigned to the gemcitabine group received gemcitabine at a dose of 1000 mg m^2 over 30 min on days 1, 8 and 15, every 4 weeks for 3 cycles. Between 2002 and 2005, 119 patients were enrolled in this study. Among them, 118 were eligible and analysable (58 in the gemcitabine group and 60 in the surgery-only group). Both groups were well balanced in terms of baseline characteristics. Although heamatological toxicity was frequently observed in the gemcitabine group, most toxicities were transient, and grade 3 or 4 non-heamatological toxicity was rare. Patients in the gemcitabine group showed significantly longer disease-free survival than those in the surgery-only group (median disease-free survival, 11 vs 5 months; hazard ratio 0.60, 95 % confidence interval 0.40 to 0.89), although overall survival did not differ significantly between the gemcitabine and surgery-only groups (median overall survival, 22 vs 18 months; hazard ratio 0.77, 95 % confidence interval 0.51 to 1.14). It was concluded that in this study adjuvant gemcitabine contributeed to prolonged disease-free survival in patients undergoing macroscopically curative resection of pancreatic cancer [123].

It was tested the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more in an open, multicenter, randomized controlled phase 3 trial with stratification for resection, tumor, and node status, conducted from 1998 to 2004 in the outpatient setting at 88 academic and community-based oncology centers in Germany and Austria. A total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation

or chemotherapy were enrolled into 2 groups. Patients received adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks (n=179), or observation (n=175). Primary end point was disease-free survival, and secondary end points were overall survival, toxicity, and quality of life. Survival analysis was based on all eligible patients (intention-to-treat). More than 80 percent of patients had R0 resection. The median number of chemotherapy cycles in the gemcitabine group was 6 (range, 0-6). Grade 3 or 4 toxicities rarely occurred with any difference in quality of life (by Spitzer index) between groups. During median follow-up of 53 months, 133 patients (74 %) in the gemcitabine group and 161 patients (92 %) in the control group developed recurrent disease. Median disease-free survival was 13 months in the gemcitabine group (95 % confidence interval, 11-15) and 7 months in the control group (95 % confidence interval, 6-8; $p<0.001$, log-rank). Estimated disease-free survival at 3 and 5 years was 24 percent and 17 percent in the gemcitabine group, and 8 percent and 6 percent in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group (median, 22 months; 95 % confidence interval, 18-26; estimated survival, 34 % at 3 years and 23 % at 5 years) and the control group (median, 20 months; 95 % confidence interval, 17-23; estimated survival, 21 % at 3 years and 12 % at 5 years; $p=0.06$, log-rank). The authors concluded that postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone [124].

Comment: The figures are impressive regarding disease-free survival and recurrent disease – which is in accordance with the larger ESPAC study – but it is depressing that the difference in overall survival still does not reach statistical significance.

Summary: Gemcitabine is useful as adjuvant in resected pancreatic cancer, but it is still not good enough.

AMF (5-fluorouracil, doxorubicin, and mitomycin C)

Between 1984 and 1987, 61 radically resected patients with carcinoma of the pancreas (n=47) or the papilla of Vater (n=14) were randomised either into postoperative adjuvant combination chemotherapy (AMF); 5-fluorouracil 500 mg/m^2, doxorubicin 40 mg/m^2, mitomycin C 6 mg/m^2 (n=30) once every 3 weeks for six cycles, or into a control group (no adjuvant chemotherapy) (n=31). The median survival in the treatment group was 23 months compared with 11 months in the control group, which was a significant difference, dependent on a survival benefit in the treatment group during the initial 2 years. The long-term prognosis was the same with an identical survival after 2 years. The observed 1, 2, 3 and 5-year survivals in the treatment group were 70, 43, 27 and 4 percent compared with 45, 32, 30 and 8 percent in the control group. One patient succumbed to sepsis probably attributable to chemotherapy. Cardiotoxicity and nephrotoxicity were recorded in 2 patients [125].

Summary: AMF is useful as adjuvant in resected pancreatic cancer, but it is still not good enough.

5-FU and radiotherapy

The survival benefit of adjuvant radiotherapy and 5-fluorouracil versus observation alone after surgery was investigated in patients with pancreatic head and periampullary cancers as a previous study of adjuvant radiotherapy and chemotherapy in these cancers by the Gastrointestinal Tract Cancer Cooperative Group of EORTC has been followed by other studies with conflicting results. Eligible patients with T1-2N0-1aM0 pancreatic head or T1-3N0-1aM0 periampullary cancer and histologically proven adenocarcinoma were randomized

after resection. Between 1987 and 1995, 218 patients were randomized (108 patients in the observation group, 110 patients in the treatment group). Eleven patients were ineligible (five in the observation group and six in the treatment group). Baseline characteristics were comparable between the two groups. One hundred fourteen patients (55 %) had pancreatic cancer (54 in the observation group and 60 in the treatment group). In the treatment arm, 21 patients (20 %) received no treatment because of postoperative complications or patient refusal. In the treatment group, only minor toxicity was observed. The median duration of survival was 19 months for the observation group and 25 months in the treatment group which was a not significant difference. The 2-year survival estimates were 41 percent and 51 percent, respectively. The results when stratifying for tumor location showed a 2-year survival rate of 26 percent in the observation group and 34 percent in the treatment group (not statistically different) in pancreatic head cancer; in periampullary cancer, the 2-year survival rate was 63 percent in the observation group and 67 percent in the treatment group. No reduction of locoregional recurrence rates was apparent in the groups. The authors concluded that adjuvant radiotherapy in combination with 5-fluorouracil is safe and well tolerated, but the benefit in this study was small and routine use of adjuvant chemoradiotherapy is not warranted as standard treatment in cancer of the head of the pancreas or periampullary region [126].

A second report report presented the long-term follow-up results of EORTC trial 40891, which assessed the role of chemoradiation in resectable pancreatic cancer. Two hundred eighteen patients were randomized after resection of the primary tumor. Eligible patients had T1-2 N0-N1a M0 pancreatic cancer or T1-3 N0-N1a M0 periampullary cancers, all histologic proven. Patients in the treatment group (n=110) underwent postoperative chemoradiation (40 Gy plus 5-FU). Patients in the control group (n=108) had no further adjuvant treatment. After a median follow-up of 12 years, 173 deaths (79 %) have been reported. The overall survival did not differ between the 2 treatment groups (chemoradiation treatment vs controls: death rate ratio 0.91; 95 % confidence interval 0.68 to 1.23). The 10-year overall survival was 18 percent in the whole population of patients (8 % in the pancreatic head cancer group and 29 % in the periampullary cancer group). These results confirm the previous short-term analysis, indicating no benefit of adjuvant chemoradiation over observation in patients with resected pancreatic cancer or periampullary cancer. Patients with pancreatic cancer may survive more than 10 years. Only 1 of 31 cases recurred after year 7 [127].

> *Comment: In this large and ambitious study it was only succeded to recruit 218 patients in 9 years, i.e. about two patients a month. As the study took so long time to complete there is a questionmark if the same techniques should have been used if the study was done today. Also, after the recruitment of 218 patients there is a tendency to better results in the treatment arm – if more patients had been included the differences reported might have been statistically significant.*

The efficacy of combined radiation and fluorouracil as adjuvant therapy for pancreatic cancer is suggested by a prospective randomized study conducted by the Gastrointestinal Tumor Study Group (GITSG). Twenty-two patients randomized to no adjuvant treatment and 21 to combined therapy were analyzed. Neither life-threatening toxic reaction nor death due to toxic effect was encountered. The study was terminated prematurely because of an unacceptably low rate of accrual combined with the observation of increasingly large survival differences between the study arms. Median survival for the treatment group (20 months) was significantly longer than that observed for the control group (11 months). Four patients, three in the treated and one in the control group, have survived five years or longer following surgery. The extent of the tumor and initial performance status were significantly and independently related to survival [128].

5FU and cisplatin

Patients with invasive ductal pancreatic cancer who underwent radical surgery with clear histological margins at 11 Japanese institutions were enrolled and randomly assigned to one of two groups: surgery-alone group (no further treatment after surgery) and the surgery + chemotherapy group (two courses of postoperative adjuvant systemic chemotherapy with cisplatin, 80 mg/m^2 day 1 and 5-fluorouracil, 500 mg/m^2/day, days 1-5). Patients with a positive resectional margin or with resected distant metastases were excluded from the trial in order to minimize the influence of residual cancer. Between 1992 and 2000, 89 patients were randomized into the two arms of the trial (45 patients to the surgery + chemotherapy arm and 44 patients to the surgery-alone arm). Four patients in total were found to be ineligible (three in the surgery + chemotherapy group and one in the surgery-alone group). The baseline characteristics were comparable between the two groups. In the surgery + chemotherapy group, four patients did not receive the adjuvant treatment because of patient refusal. Toxicity was minor and acceptable among the eligible patients in the surgery + chemotherapy group. The estimated 5-year survival rates were 27 percent in the surgery + chemotherapy group and 15 percent in the surgery-alone group, and the median duration of survival was 13 months and 16 months, respectively. The recurrence rates at 5 years were 74 and 81 percent, respectively, in the surgery + chemotherapy and the surgery-alone groups. The differences in the survival and recurrence rates between the two groups were not statistically significant. This means that postoperative adjuvant chemotherapy using cisplatin and 5-fluorouracil was safe and well tolerated; however, no clear survival benefit could be demonstrated [129].

5FU and mitomycin C

A randomized controlled study evaluated the effect of postoperative adjuvant therapy with mitomycin C (MMC) and 5-fluorouracil (5-FU) (MF arm) versus surgery alone (control arm) on survival and disease-free survival for each specific disease comprising resected pancreaticobiliary carcinoma (pancreatic, gallbladder, bile duct, or ampulla of Vater carcinoma) separately. Between 1986 and 1992, a total of 508 patients with resected pancreatic (n=173), bile duct (n=139), gallbladder (n=140), or ampulla of Vater (n=56) carcinomas were allocated randomly to either the MF group or the control group. The MF group received MMC (6 mg/m^2 intravenously) at the time of surgery and 5-FU (310 mg/m^2 i.v.) in 2 courses of treatment for 5 consecutive days during postoperative weeks 1 and 3, followed by 5-FU (100 mg/m^2 orally) daily from postoperative week 5 until disease recurrence. All patients were followed for 5 years. After ineligible patients were excluded, 158 patients with pancreatic carcinoma (81 in the MF group and 77 in the control group were evaluated. Good compliance (> 80 %) was achieved with MF treatment. The 5-year survival rate in gallbladder carcinoma patients was significantly better in the MF group (26 %) compared with the control group (14 %). There were no apparent differences in 5-year survival and 5-year disease-free survival rates between patients with pancreatic, bile duct, or ampulla of Vater carcinomas. Multivariate analyses demonstrated a tendency for the MF group to have a lower risk of mortality (risk ratio of 0.654; p=0.08) and recurrence (risk ratio of 0.626; p=0.06). The most commonly reported adverse drug reactions were anorexia, nausea/emesis, stomatitis, and leukopenia, none of which were noted to be serious. The

results of the current study indicate that patients with carcinomas of the pancreas did not benefit from mitomycin C and 5-fluorouracil in the adjuvant setting [130].

5FU-based chemoradiation therapy

The objective of one study was to determine the effect, if any, on survival of adjuvant 5-FU-based chemoradiotherapy following pancreaticoduodenectomy for pancreatic carcinoma. A systematic review of the published literature was undertaken. Survival estimates were derived from published reports. Five prospective studies (4 level I, 1 level II) with a total of 607 (229 surgery only; 378 surgery-adjuvant) patients followed for survival met selection criteria. Two-year survival ranged from 15 percent to 37 percent in the surgery only group and 37 percent to 43 percent in the surgery and adjuvant groups. The survival advantage (absolute difference) ranged from 3 percent to 27 percent and no individual study achieved statistical significance (5 %). Although clinical heterogeneity existed in surgery-alone control groups with regard to trial date, no statistical heterogeneity was, allowing pooling of survival data. Using a fixed effects model, the summary estimate showed an absolute 2-year survival benefit with adjuvant therapy of 12 percent (95 % confidence interval 3 to 21 %). Trials after 1997 (n=3) indicated a survival benefit of 8 percent to patients receiving adjuvant therapy (95 % confidence interval -3 to 18 percent). The result was not statistically significant, and there was no evidence of heterogeneity. Summary estimates were unchanged when the analysis was performed with a random effects model. 5-FU based chemotherapy with radiotherapy given after resection imparts a small overall survival benefit of 2 years. The benefit of 5-FU-based adjuvant therapy, however, has declined in recent years, and its significance remains unproven in the context of current diagnostic and surgical practice [131].

> Comment: It is of interest that there are indications that 5FU-based adjuvant therapy has less good effects in recent years, which makes it probable that its effects before have been overestimated.

Chemoradiotherapy

Though the outcome of resection for locally invasive pancreatic cancer is still poor, it has gradually improved in Japan, and the 5-year survival was in 2004 about 10 percent. However, the advantage of resection over radiochemotherapy has not yet been confirmed by a randomized trial. It was conducted a study to compare surgical resection alone versus radiochemotherapy without resection for locally invasive pancreatic cancer using a multicenter randomized design. Patients with pancreatic cancer who met the preoperative criteria for inclusion (pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric artery or the common hepatic artery, or without distant metastasis) underwent laparotomy. Patients with operative findings consistent with our criteria were randomized into a radical resection group and a radiochemotherapy group (200 mg/m^2/day of intravenous 5-fluorouracil and 5040 cGy of radiotherapy) without resection. The two groups were compared for mean survival, hazard ratio, 1-year survival, quality of life scores, and hematologic and blood chemical data. Twenty patients were assigned to the resection group and 22 to the radiochemotherapy group. There was one operative death. The surgical resection group had significantly better results than the radiochemotherapy group as measured by 1-year survival (62 % vs 32 %), mean survival time (>17 vs 11 months), and hazard ratio (0.46). There were no differences in the quality of life score or laboratory data apart from increased diarrhea after surgical resection. Locally invasive pancreatic cancer without distant metastases and major arterial invasion appears to be best treated by surgical resection [132].

Among patients with locally advanced metastatic pancreatic adenocarcinoma, gemcitabine has been shown to improve outcomes compared with fluorouracil. To determine if the

addition of gemcitabine to adjuvant fluorouracil chemoradiation (chemotherapy plus radiation) improves survival for patients with resected pancreatic adenocarcinoma a randomized controlled phase III trial of patients with complete gross total resection of pancreatic adenocarcinoma and no prior radiation or chemotherapy were performed. Between 1998 and 2002 with follow-up through August 2006 at 164 US and Canadian institutions chemotherapy with either fluorouracil (continuous infusion of 250 mg/m^2 per day; n=230) or gemcitabine (30-minute infusion of 1000 mg/m^2 once per week; n=221) for three weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation therapy was given. Chemoradiation with a continuous infusion of fluorouracil (250 mg/m^2 per day) was the same for all patients (50.4 Gy). Survival for all patients and survival for patients with pancreatic head tumors were the primary end points. Secondary end points included toxicity. A total of 451 patients were randomized, eligible, and analyzable. Patients with pancreatic head tumors (n=388) had a median survival of 21 months and a 3-year survival of 31 percent in the gemcitabine group versus a median survival of 17 months and a 3-year survival of 22 percent in the fluorouracil group (hazard ratio, 0.82; 95 % confidence interval 0.65 to 1.03). The treatment effect was strengthened on multivariate analysis (hazard ratio 0.80; 95 % confidence interval 0.63 to 1.00). Grade 4 hematologic toxicity was 1 percent in the fluorouracil group and 14 percent in the gemcitabine group, which was a significant difference, but without a difference in febrile neutropenia or infection. There were no differences in the ability to complete chemotherapy or radiation therapy (>85 %). It was concluded that the addition of gemcitabine to adjuvant fluorouracil-based chemoradiation was associated with a survival benefit for patients with resected pancreatic cancer, although this improvement was not statistically significant [133].

Comment: This rather large study with long follow-up does not convincingly indicate that the combination of gemcitabine and 5-fluorouracil is of value.

Cytostatics and immunotherapy

A prospective randomized clinical trial combining adjuvant locoregional chemo-immunotherapy for pancreatic carcinoma in 512 patients was conducted from 1991 to 1998 at Athens Medical Center. All patients were randomly assigned to (A) Resective Surgery (n=274), and (B) Palliative Surgery (n=238) groups. Each group was further subdivided into: (1) surgery alone, and (2) surgery plus 1-day bolus chemotherapy (gemcitabine 1 gm/m^2, carboplatin 200 mg/m^2 and mitoxantrone 0.2 g/kg bw suspended in 10 ml of Lipiodol and 2 ml of 58 % urografin), and immunotherapy (1 ml interleukin-2 and 0.5 ml gamma-interferon suspended in 5 ml of Lipiodol and 1 ml of 58 % urografin) followed by a 5-day course of transplenic and another 5-day course of transtumoral immunotherapy using the same agents. This was repeated at 2-month intervals during the first post-operative year and every 3 months thereafter. Significant reduction in patient symptomatology and improvements in post-treatment quality of life were noted in patients receiving adjuvant chemoimmunotherapy. Moreover, the mean survival rate significantly improved in patients receiving the adjuvant treatment, both for the resective (32 months) and the palliative (16 months) groups [134].

Comment: This is an enormous amount of patients operated on with resective surgery in one single Greek hospital: 274 in 8 years, i.e. about 35 per year. Moreover, in most other settings only a limited part of all resected patients are finally getting the adjuvant treatment – somewhere between 1/3 and 2/3 of the possible patients never get the planned treatment. Before accepting the results completely an audit should be performed.

From the same investigators, a group of 26 patients was divided into two groups, which were matched in terms of age-sex ratio, stage of disease, histological diagnosis and mode of pancreatic resection. Group A patients received a multimodality therapy, combining

pancreatic resection with neo- and adjuvant locoregional targeting immunochemotherapy. Group B received pancreatic surgery only: For group A patients (n=14), a complete response was seen in 11 patients with a time interval ranging from 9 to 29 months. In the remaining 3 patients liver secondaries developed 12 months after pancreatic resection in 2 patients and the other patient developed pulmonary metastases 22 months after pancreatic resection. All patients (n=3) are alive, but continue to have the disease. For group B patients (n=12), a complete response was seen in 3 patients with a survival of 9, 10 and 20 months following pancreatic resection. Six patients died due to locoregional recurrence of the disease, with the survival rate ranging from 7 to 18 months (mean 10 months). Locoregional recurrence was complicated with liver secondaries (n=3) and with peritoneal dissemination of the disease in a further 3 patients. The remaining 3 patients are alive, but continue to have the disease due to locoregional recurrence [135].

Monoclonal antibodies

In a prospective randomized multicentric trial, 61 patients from six hospitals with resectable pancreatic cancer were recruited between 1987 and 1989. All patients underwent a Whipple resection. Two weeks after surgery, the patients were randomized to be given either intravenous treatment with 370 mg (100 mg loading dose, 9 x 30 mg continuing within 10 days) of monoclonal antibody 494/32 (Behringwerke AG, Marsburg, Germany) or no additional anti-cancer treatment. This murine immunoglobulin (Ig) G1 antibody has been shown to strongly bind to human pancreatic cancer cells and to induce an antibody-dependent cellular cytotoxicity (ADCC). Both study groups were well matched with respect to age, gender, tumor staging, and grading. Six patients suffered from minor toxicity (vomiting and abdominal pain) after immunotherapy. Ten months after the end of the recruitment period, 65 percent and 53 percent of the patients in the treatment and control groups, respectively, had died. Of the living patients, 60 percent and 53 percent were alive with recurrent or progressive cancer disease. Median survival time was 428 days (range, 248 to 510 days) and 386 days (range, 296 to 509 days) in the treatment and control groups, respectively. The authors concluded that repeated intravenous treatment with the antibody 494/32 is not helpful in resectable pancreatic cancer [136].

Local therapy through an arterial catheter

To evaluate in a prospective randomized study the long-term results of adjuvant locoregional chemoimmunotherapy in a number of patients with stage III pancreatic duct cancer who underwent pancreatic resection between 1993 and 2000 128 patients were divided into three groups. Group A (n=40) patients had surgical resection alone. Group B (n=45) patients had, using a side arterial branch of the jejunal artery, an arterial catheter advanced under fluoroscopic control into the superior mesenteric artery. Group B patients also received adjuvant chemotherapy. Group C (n=43) patients had the same kind of arterial catheter and received as an adjuvant treatment locoregional chemoimmunotherapy. During the initial surgical exploration, all patients underwent pancreatic resection. Pancreatic resection involved a standard technique of extended duodenopancreatectomy with regional lymphadenectomy and was carried out in all patients by the first author. At the end of intervention, all patients were randomly assigned to the above-mentioned groups. Randomization was based mainly on histologic evidence of the stage of the disease. The 2- and 5-year survival rates were 29 percent and 0 percent for group A, 52 percent and 10 percent for group B, and 65 percent and 18 percent for group C. The respective percentages for disease-free survival were 20 percent and 0 percent for group A, 35 percent and 7 percent for group B, and 58 percent and 11 percent for group C. Since statistical differences among groups were observed from the second and third years, the study was interrupted early for ethical reasons [137].

Success of surgical treatment for pancreatic and periampullary cancer is often limited due to locoregional recurrence and/or the development of distant metastases. The survival benefit of celiac axis infusion (CAI) and radiotherapy (RT) versus observation after resection of pancreatic or periampullary cancer was therefore investigated. In a randomized controlled trial, 120 consecutive patients with histopathologically proven pancreatic or periampullary cancer received either adjuvant treatment consisting of intra-arterial mitoxantrone, 5-FU, leucovorin, and cisplatinum in combination with 30 x 1.8 Gy radiotherapy (group A) or no adjuvant treatment (group B). Groups were stratified for tumor type (pancreatic vs. periampullary tumors). After surgery, 120 patients were randomized (59 patients in the treatment group, 61 in the observation group). The median follow-up was 17 months. No significant overall survival benefit was seen (median, 19 vs 18 months). Progressive disease was seen in 86 patients: in 37 patients in the CAI/RT group, and in 49 patients in the observation group. Subgroup analysis showed significantly less liver metastases after adjuvant treatment in periampullary tumors without effect on local recurrence. Nonetheless, there was no significant effect on overall survival in these patients. In patients with pancreatic cancer, CAI/RT had no significant effect on local recurrence neither on the development of liver metastases and consequently, no effect on overall survival. The authors concluded that this adjuvant treatment schedule results in a prolonged time to progression. For periampullary tumors, CAI/RT induced a significant reduction in the development of liver metastases, with a possible effect on overall survival [138].

> *Comment: The two studies are reasonable large and are both positive. In further studies this treatment should be randomized against the more easy adjuvant treatments.*

Tamoxifen

It was found high levels of estrogen receptor in 21 cases out of 27 carcinomas of the pancreas (78 %). Therefore, the patients were randomly given hormone therapy by Tamoxifen 20 mg per day adding to immuno-chemotherapy (Tegaful, Mitomycin, Krestin, OK-432) to the patients with resected carcinoma of the pancreas. There was no significant difference of the survival rate of pancreatic carcinoma without hormone therapy between 10 cases with estrogen receptor and 4 cases without estrogen receptor at the 6th month and 12th month. However, in cases treated by Tamoxifen, remarkable high survival rate at 12 months of 11 cases with estrogen receptor was obtained to be 86 percent. Two cases without estrogen receptor died within 5 months. One year survival rate of Tamoxifen group (13 cases) was 79 percent and that of non Tamoxifen group (14 cases) was 21 percent [139].

> *Comment: interesting, but much too small study. As it has not been followed-up since 1993 indicates that there was some disadvantage hidden.*

Meta-analysis

In patients undergoing surgery for resectable pancreatic cancer prognosis still remains poor. The role of adjuvant treatment strategies (including chemotherapy and chemoradiotherapy) following resection of pancreatic cancer remains controversial. A Medline-based literature search was undertaken to identify randomized controlled trials that evaluated adjuvant chemotherapy after complete macroscopic resection for cancer of the exocrine pancreas. Five trials of adjuvant chemotherapy were eligible and critically reviewed for this article. A meta-analysis (based on published data) was performed with survival (median survival time and 5-year survival rate) being the primary endpoint. For the meta-analysis, 482 patients were allocated to the chemotherapy group and 469 patients to the control group. The meta-analysis estimate for prolongation of median survival time for patients in the chemotherapy

group was 3 months (95 % confidence interval 0.3 to 5.7 months). The difference in 5-year survival rate was estimated with 3.1 percent between the chemotherapy and the control group (95 % confidence interval -4.6 to 10.8 %). It was concluded that currently available data from randomized trials indicate that adjuvant chemotherapy after resection of pancreatic cancer may substantially prolong disease-free survival and cause a moderate increase in overall survival. In the current meta-analysis, a significant survival benefit was only seen with regard to median survival, but not for the 5-year survival rate. The optimal chemotherapy regimen in the adjuvant setting as well as individualized treatment strategies (also including modern chemoradiotherapy regimens) still remain to be defined [140].

> *Summary: This meta-analysis shows that adjuvant chemotherapy should be recommended.*

Influence of resection margins (a meta-analysis)

To assess the influence of resection margins and adjuvant chemoradiotherapy or chemotherapy on survival for patients with pancreatic cancer by meta-analysis of individual data from randomized controlled trials. A structured MEDLINE search for published studies was performed. Individual data were obtained from four published trials (875 patients: 278, 32 %, with R1 and 591, 68 %, with R0 resections). Kaplan-Meier estimates of survival were compared using log-rank analyses. Pooled hazard ratios of the effects of chemoradiotherapy and chemotherapy treatments on the risk of death were calculated separately and across groups according to resection margins status. Six hundred ninety-eight patients (80 %) had died, with a median follow-up of 44 months in the surviving patients. Resection margin involvement was not a significant factor for survival (hazard ratio 1.10; 95 % confidence interval 0.94 to 1.29). The 2- and 5-year survival rates, respectively, were 33 percent and 16 percent for R0 patients and 29 percent and 15 percent for R1 patients. Chemoradiotherapy in R1 patients resulted in a 28 percent reduction in the risk of death (hazard rate 0.72; 95 % confidence interval 0.47 to 1.10) compared with a 19 percent increased risk in R0 patients (hazard rate 1.19; 95 % confidence interval 0.95 to 1.49). Chemotherapy in R1 patients had a 4 percent increased risk of death (hazard rate 1.04; 95 % confidence interval 0.78 to 1.40) compared with a 35 percent reduction in risk in the R0 subgroup (hazard rate 0.65; 95 % confidence interval 0.53 to 0.80). It was concluded that adjuvant chemotherapy but not chemoradiotherapy should be the standard of care for patients with either R0 or R1 resections for pancreatic cancer [141].

> *Comment: The result of this large meta-analysis shows that chemotherapy should be given after a pancreatic cancer resection both to patients in R0 and R1.*

Neoadjuvant treatment

In a randomized phase II study compares gemcitabine-based neoadjuvant chemotherapy regimens to identify the most promising regimen for future study. Fifty patients with potentially resectable pancreas lesions were enrolled onto the study. Twenty-four patients were randomized to gemcitabine (1000 mg/m^2) every 7 days for 43 days; 26 patients were randomized to gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), 7 to the original schedule (omitting day 22) and 19 to a revised schedule due to neutropenia (omitting days 15 and 36). The primary outcome measure was resection rate. Patients who were allocated to gemcitabine received a median of 85 percent of the planned dose. Patients who were allocated to combination treatment received a median of 88 percent and 92 percent of the planned gemcitabine and cisplatin doses, respectively. There were 10 episodes of grade III/IV hematological toxicity in each group. Twenty-seven patients (54 %) underwent pancreatic resection, 9 (38 %) in the gemcitabine arm and 18 (70 %) in the combination arm,

with no increase in surgical complications. To date of publication, 34 patients (68 %) had died. Twelve-month survival for the gemcitabine and combination groups was 42 percent and 62 percent, respectively. The authors concluded that a combination therapy with gemcitabine and cisplatin is associated with a high resection rate and an encouraging survival rate [142].

Comment: The study is much too small – maybe it can be used as introduction of the hypothesis to other researchers.

Single Gemcitabine for advanced cancer

A prospective, randomized study was performed to determine whether gemcitabine infusion at a low dose (250 mg/m^2) is comparable or superior to the standard-dose infusion (1000 mg/m^2) in terms of the survival period, clinical benefit, and frequency of adverse effects in patients with advanced pancreatic adenocarcinoma. Twenty-five patients who were histologically proven to have locally advanced pancreatic cancer or pancreatic cancer with distant metastases were initially enrolled in the study. They were treated with gemcitabine infusion at either a dose of 1000 mg/m^2 over 30 min (the standard regimen) on days 1, 8, and 15 of every 4-week cycle or at a dose of 250 mg/m^2 over 30 min every week. Survival time, response rate, time to treatment failure, clinical benefit response, and adverse effects were compared between the two groups. Twenty-one patients received gemcitabine for more than 1 month. The median survival period was 7 months for patients who received the low-dose infusion regimen, in contrast to 5 months for patients administered the standard-dose infusion regimen. The time to treatment failure was 6 months for patients in the low-dose infusion regimen, in contrast to 3 months for patients in the standard-dose infusion regimen. There were no significant differences in either survival time to time to treatment failure or clinical benefits between the two groups, but the incidence of adverse reactions in patients administered the low-dose therapy was significantly lower than that in patients receiving the standard-dose therapy. In particular, patients in the standard infusion regimen group experienced more hematologic toxicity than those in the low-dose regimen [143].

It was evaluated the efficacy of gemcitabine as palliative treatment in patients with advanced pancreatic cancer previously treated with placement of a covered metal biliary stent, taking into account survival and quality of life. Forty-nine patients with unresectable pancreatic cancer and obstructive jaundice, previously treated with the placement of a covered metal biliary endoprosthesis, were randomized to receive gemcitabine (group A: 9 males, 7 females) or to be followed without any anticancer intervention (group B: 18 males, 15 females). Gemcitabine was administered weekly as intravenous 30 min infusion of 1000 mg/m^2 for 3 consecutive weeks followed by 1-week rest (28-day cycle). QoL was evaluated with the QLQ-C30 questionnaire. 229 gemcitabine doses were administered (median doses per patient 14, range 7-22). No statistically significant differences were observed regarding survival (group A: median 21 weeks, range 13-33; group B: median 22 weeks, range 13-29). According to the average QLQ-C30 score, group B patients showed statistically significant higher values. Leukopenia, neutropenia, thrombocytopenia and anemia were the most common side effects in group A (81, 69, 62 and 31 %, respectively). It was concluded that gemcitabine did not show to improve survival and quality of life in patients with advanced pancreatic cancer previously treated with a covered metallic biliary endoprosthesis due to obstructive jaundice [144].

Comment: Two rather disappointing studies on gemcitabine alone.

Fixed dose rate

In a prospective trial, patients with locally advanced and metastatic pancreatic adenocarcinoma were treated with 2,200 mg/m^2 gemcitabine over 30 minutes (standard arm) or 1,500 mg/m^2 gemcitabine over 150 minutes fixed dose rate (FDR arm) (10 mg/m^2/min) on days 1, 8, and 15 of every 4-week cycle. The primary end point of this trial was time to treatment failure. Secondary end points included time to progression, median survival, safety, and pharmacokinetic studies of gemcitabine. Ninety-two patients were enrolled onto this study; 91 percent of the patients had metastatic disease. Time to treatment failure was comparable in both treatment groups; however, the median survival for all patients was 5 months in the standard arm and 8 months in the FDR arm, which is a significant difference. For patients with metastases, the median survival was 5 months in the standard arm and 7 months in FDR arm (not significant different statistically). The 1- and 2-year survival rates for all patients were 9 percent (standard arm) versus 29 percent (FDR) and 2.2 percent (standard arm) versus 18 percent (FDR), respectively, which were significant differences. Patients in the fixed dose rate infusion arm experienced consistently more hematologic toxicity. Pharmacokinetic analyses demonstrated a significant, two-fold increase in intracellular gemcitabine triphosphate concentration in the FDR arm. This means that pharmacokinetic and clinical data in this trial supports the continued evaluation of the fixed dose rate infusion strategy with Gemcitabine [145].

> *Comment: This study is very important from several points of view. One of them is that our protocols for chemotherapy might be more intelligently structured if we base them on science, another that "more" is not necessarily better.*

Gemcitabine compared to other cytostatics

Gemcitabine versus 5-fluorouracil

One hundred twenty-six patients with advanced symptomatic pancreas cancer completed a lead-in period to characterize and stabilize pain and were randomized to receive either gemcitabine 1,000 mg/m^2 weekly x 7 followed by 1 week of rest, then weekly x 3 every 4 weeks thereafter (63 patients), or to fluorouracil (5-FU) 600 mg/m^2 once weekly (63 patients). The primary efficacy measure was clinical benefit response, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained ($\geq$ 4 weeks) improvement in at least one parameter without worsening in any others. Other measures of efficacy included response rate, time to progressive disease, and survival. Clinical benefit response was experienced by 24 percent of gemcitabine-treated patients compared with 5 percent of 5-FU-treated patients, which was a significant difference. The median survival durations were 6 and 4 months for gemcitabine-treated and 5-FU-treated patients, respectively, which also was a statistically significant difference. The survival rate at 12 months was 18 percent for gemcitabine patients and 2 percent for 5-FU patients. Treatment was well tolerated [146].

In a randomised study by the same group as above but published a year earlier, the clinical benefit response rate for gemcitabine was 24 percent compared with 5 percent for 5-fluorouracil (5-FU), which was a significant difference. The median survival was 6 months for gemcitabine compared with 4 months for 5-FU, which was also significantly different. The corresponding objective response rates were 5 percent and 0 percent. Disease stabilised in 39 percent and 19 percent of gemcitabine and 5-FU patients, respectively [147].

> *Summary:* If *there are significant clinical differences, gemcitabine seems to be better than 5FU.*

Gemcitabine versus 5-fluorouracil at concomitant chemoradiotherapy

To determine the efficacy and tolerability of gemcitabine (GEM) and concurrent chemoradiotherapy (CRT) versus 5-fluorouracil (5-FU) concurrent CRT for locally advanced pancreatic cancer. Thirty-four patients with locally advanced pancreatic cancer were studied. Eighteen patients were randomized to receive GEM CCRT (600 mg/m^2/week for 6 weeks) and 16 patients to receive bolus 5-FU CRT (500 mg/m^2/day for 3 days repeated every 2 weeks for 6 weeks). All patients were to receive 3D-CRT 50.4-61.2 Gy at 1.8-Gy/d fractions and GEM (1000 mg/m^2 weekly for 3 weeks repeated every 4 weeks) after radiotherapy. The median survival and median time to progression were 15 months and 7 months for the GEM CRT group and 7 months and 3 months for the 5-FU CRT group, respectively, which was significant differences. The quality-adjusted life month survival time was 11.2 $\pm$ 0.5 months for GEM CRT and 6.0 $\pm$ 0.3 months for 5-FU CRT patients, which also was a significant difference. The response rate was 50 percent (four complete responses and five partial responses) for GEM CRT and 13 percent (two partial responses) for 5-FU CRT, i.e. significant difference. Pain control was 39 percent for GEM CRT and 6 percent for 5-FU CRT (p=0.04). Grade 3-4 neutropenia (34 % vs 19 %), thrombocytopenia (0 % vs 7 %), nausea (33 % vs 31 %), vomiting (17 % vs 19 %), hospitalization days per month of survival (7 $\pm$ 2 days vs 8 $\pm$ 1 days), and full dose of radiotherapy received (78 % vs 75 %) were not significantly different between the GEM CRT and 5-FU CRT patients. The authors concluded that gemcitabine together with chemoradiotherapy was more effective than 5-FU chemoradiotherapy for locally advanced pancreatic cancer [148].

Within a multi-centre, randomised phase II trial, 95 patients with locally advanced pancreatic cancer were assigned to three different chemoradiotherapy (CRT) regimens: patients received conventionally fractionated radiotherapy of 50 Gy and were randomised to concurrent 5-fluorouracil (350 mg/m^2 per day on each day of radiotherapy, RT-5-FU arm), concurrent gemcitabine (300 mg/m^2), and cisplatin (30 mg/m^2) on days 1, 8, 22, and 29 (RT-GC arm), or the same concurrent treatment followed by sequential full-dose gemcitabine (1000 mg/m^2) and cisplatin (50 mg/m^2) every 2 weeks (RT-GC+GC arm). Primary end point was the overall survival (OS) rate after 9 months. The 9-month overall survival rate was 58 percent in the RT-5-FU arm, 52 percent in the RT-GC arm, and 45 percent in the RT-GC+GC arm. Corresponding median survival times were 10, 9, and 7 months, respectively. The intent-to-treat response rate was 19, 22, and 13 percent, respectively. Median progression-free survival was estimated with 4, 6, and 6 months (a not significant difference). Grade 3/4 haematological toxicities were more frequent in the two GC-containing arms, no grade 3/4 febrile neutropaenia was observed. It was concluded that none of the three CRT regimens tested met the investigators' definition for efficacy; the median OS was similar to those previously reported with gemcitabine alone in locally advanced pancreatic cancer [149].

> *Summary: Summary:* If *there are clinical differences, gemcitabine seems to be just as good or better than 5FU.*

Gemcitabine versus matrix metalloproteinase inhibitor

To compare the selective matrix metalloproteinase inhibitor BAY 12-9566 with the nucleoside analog gemcitabine in the treatment of advanced pancreatic cancer patients with advanced pancreatic adenocarcinoma who had not previously received chemotherapy were randomly assigned to receive BAY 12-9566 800 mg orally bid continuously or gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, 15, 22, 29, 36, and 43 for the first 8 weeks, and then days 1, 8, and 15 of each subsequent 28-day cycle. The primary end point was overall survival; secondary end points were progression-free survival, tumor response,

quality of life, and clinical benefit. The planned sample size of the study was 350 patients. Two formal interim analyses were planned. The study was closed to accrual after the second interim analysis on the basis of the recommendation of the National Cancer Institute of Canada Clinical Trials Group Data Safety Monitoring Committee. There were 277 patients enrolled onto the study, 138 in the BAY 12-9566 arm and 139 in the gemcitabine arm. The rates of serious toxicity were low in both arms. The median survival for the BAY 12-9566 arm and the gemcitabine arm was 4 months and 7 months, respectively, which was a significant difference. The median progression-free survival for the BAY 12-9566 and gemcitabine arms was 2 and 4 months, which also was a significant difference. Quality-of-life analysis also favored gemcitabine [150].

Four hundred fourteen patients with unresectable pancreatic cancer were randomized to receive marimastat 5, 10, or 25 mg bid or gemcitabine 1,000 mg/m^2. The primary end point was survival. There was no significant difference in survival between 5, 10, or 25 mg of marimastat and gemcitabine. Median survival times were 111, 105, 125, and 167 days, respectively, and 1-year survival rates were 14 percent, 14 percent, 20 percent, and 19 percent, respectively. There was a significant difference in survival rates between patients treated with gemcitabine and marimastat 5 and 10 mg. Both agents were well tolerated, although grade 3 or 4 toxicities were reported in 22 percent and 12 percent of the gemcitabine- and marimastat-treated patients, respectively. The major toxicity of marimastat was musculoskeletal (44 % of marimastat patients, compared with 12 % of gemcitabine patients; musculoskeletal toxicity was severe in only 8 % of marimastat patients). The authors concluded that the results of the study provide evidence of a dose response for marimastat in patients with advanced pancreatic cancer. The 1-year survival rate for patients receiving marimastat 25 mg was similar to that of patients receiving gemcitabine [151].

A randomised study in pancreatic cancer compared marimastat (orally administered matrix metalloproteinase inhibitor) in combination with gemcitabine to gemcitabine alone. Two hundred and thirty-nine patients with unresectable pancreatic cancer were randomised to receive gemcitabine (1000 mg/m^2) in combination with either marimastat or placebo. The primary end-point was survival. Objective tumour response and duration of response, time to treatment failure and disease progression, quality of life and safety were also assessed. There was no significant difference in survival between gemcitabine and marimastat and gemcitabine and placebo. Median survival times were 166 and 164 days and 1-year survival was 18 percent and 17 percent, respectively. There were no significant differences in overall response rates (11 and 16 %, respectively), progression-free survival, or time to treatment failure between the treatment arms. The gemcitabine and marimastat combination was well tolerated with only 3 percent of patients withdrawn due to presumed marimastat toxicity [152].

Summary: There are no indications that marimastat is better then gemcitabine, but the side-effects are worse.

Gemcitabine versus FLEC

In one study, patients were randomly assigned to receive gemcitabine at a dose of 1,000 mg/m^2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 weeks every 4 weeks or 300 mg/m^2 infused bolus intra-arterially into celiac axis at a 3-week interval 3 times or 5-fluorouracil 400 mg/m^2 plus folinic acid 20 mg/m^2 for 5 days every 4 weeks for 6 cycles. The primary endpoint was overall survival, while time to treatment failure, response rate, clinical benefit response were secondary endpoints. Sixty-seven patients were randomly allocated gemcitabine and 71 were allocated FLEC intra-arterially. Patients treated with FLEC lived for significantly longer than patients on gemcitabine. Survival at 1 year increased from 21 percent in the gemcitabine group to 35

percent in the FLEC group. Median survival was 8 months in the FLEC group and 6 months in the gemcitabine group. Median time to treatment failure was significantly longer with FLEC (5 vs 4 months for FLEC vs gemcitabine, respectively). Clinical benefit was similar in both groups (18 % for gemcitabine and 27 % for FLEC). CT-scan partial response was similar in both groups (6 % for gemcitabine and 14% for FLEC). Toxicity profiles were different [153].

Gemcitabine versus FLEC given as intra-arterial combined drugs
Intra-arterial drug administration had shown a deep rationale with some interesting results. In a multicenter phase III trial, it was compared gemcitabine given weekly with a combination of 5-fluoruracil, leucovorin, epirubicin, carboplatin (FLEC) administered intra-arteriously as first-line therapy in unresectable pancreatic adenocarcinoma. Patients were randomly assigned to receive gemcitabine at a dose of 1,000 mg/m^2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 weeks every 4 weeks or 5-fluoruracil 1,000 mg/m^2, leucovorin 100 mg/m^2, epirubicin 60 mg/m^2, carboplatin 300 mg/m^2 infused bolus intra-arteriously at three-weekly interval for 3 times. The primary end point was overall survival, while time to treatment failure, response rate, clinical benefit response were secondary endpoints. Sixty-seven patients were randomly allocated gemcitabine and 71 were allocated FLEC intra-arterially. Patients treated with FLEC lived for significantly longer than patients on gemcitabine (p=0.036). Survival at 1 year was increased from 21 percent in the gemcitabine group to 35 percent in the FLEC group. Median survival was 8 months in the FLEC group and 6 months in the gemcitabine group. Median time to treatment failure was significantly longer with FLEC (5 vs 4 months for FLEC vs gemcitabine respectively). Clinical benefit was similar in both groups (18 % for gemcitabine and 27 % for FLEC). CT-scan partial response was similar in both group (6 % for gemcitabine and 14 % for FLEC; p=NS). Toxicity profiles were different [154].

> *Summary: FLEC was not better than gemcitabine alone.*

Gemcitabine versus thymidylate synthase inhibitor

ZD9331 is a novel antifolate inhibitor of thymidylate synthase (TS). In a multicentre, randomised, phase II/III study it was compared the efficacy and safety of ZD9331 with gemcitabine in 55 patients with chemonaive, locally advanced or metastatic pancreatic cancer. Patients received intravenous ZD9331 (n=30), on days 1 and 8 of a 3-week cycle or intravenous gemcitabine (n=25), once a week for 7 weeks followed by a 1-week rest, then on days 1, 8 and 15 of a 4-week cycle. Objective tumour response and clinical benefit response (CBR) were similar for both groups. More ZD9331 patients were alive at the data cut-off point compared with gemcitabine patients (13 and 8 %, respectively). Median survival (152 versus 109 days, respectively) and time to progression (70 versus 58 days, respectively) were longer in the ZD9331 group. Nausea and vomiting (grade 1/2) were the most common toxicities in both groups. These results suggest that, in pancreatic cancer, ZD9331 is equivalent to gemcitabine and may offer a promising alternative to current therapies [155].

> *Summary: an antifolate inhibitor of thymidylate synthase was not better than gemcitabine alone.*

Gemcitabine versus imatinib

Imatinib targets KIT and platelet-derived growth factor receptors (PDGFR) and is highly effective in the treatment of chronic myeloic leukemia, CML, and gastrointestinal stromal tumor, GIST, patients. Pancreatic cancers express KIT and PDGFRs. Therefore, 26 patients with unresectable pancreatic cancer were randomized to either gemcitabine (1000 mg/m^2 weekly) or imatinib (2x400 mg po) treatment daily. Pancreatic adenocarcinoma was confirmed histologically and expression of KIT and PDGFRbeta was determined

immunohistochemically in the biopsy specimens. Quality of life was assessed with two standard questionnaires. No objective responses were seen in either group. Median time to progression was 77 and 29 days, which was a not statistically significant difference, and median survival time was 140 and 60 days (dito) for gemcitabine and imatinib, respectively. Survival and treatment responses were independent of KIT and PDGFRbeta expression in patients treated with imatinib. Grade 3/4 toxicities of imatinib treatment were anemia, elevated liver enzymes, vomiting, and dyspnea. Patients treated with imatinib reported diarrhoea and/or altered bowel function more frequently, which were treatable symptomatically. Quality of life was similar in both groups. In this small series of pancreatic cancer patients, treatment with imatinib was not associated with a significant control of cancer progression [156].

> *Comment: This study is gravely underpowered, and if just a limited number of patients could be added the strong trend should probably be statistically significant. However, from an intellectual point of view it is disappointing that there is no correlation between KIT and PDGFR expression and respons to imatinib.*

Gemcitabine $\pm$ combinations for advanced disease

Gemcitabine $\pm$ 5-fluorourail

A study was performed to determine the activity of adding continuous infusion of 5-fluorouracil (5-FU) to gemcitabine (GEM) versus gemcitabine alone in advanced pancreatic cancer. In all, 94 chemo-naïve patients with advanced pancreatic cancer were randomised to receive GEM alone (arm A: 1000 mg m^2 per week for 7 weeks followed by a 2 week rest period, then weekly for 3 consecutive weeks out of every 4 weeks) or in combination with continous infusion of 5-FU (arm B: 5-FU 200 mg m^2 per day for 6 weeks followed by a 2 week rest period, then for 3 weeks every 4 weeks). Overall response rate was the primary end point. The overall response rate was 8 response (arm A) and 11 percent (arm B) (95 % confidence interval: 0.5-16 % and 2-22 %), respectively, and stable disease was 29 and 28 percent. The median duration of response rate was 34 weeks (range 25-101 weeks) for gemcitabine and 26 weeks (range 16-46 weeks) for the combination. The median progression-free survival was 14 weeks (range 2-65 weeks) and 18 weeks (range 4-51 weeks), respectively. The median overall survival was 31 weeks (range 1-101 weeks) and 30 weeks (1-101 weeks). Toxicity was mild in both arms [157].

To find out whether the addition of fluorouracil improves on the results from single-agent gemcitabine, the Eastern Cooperative Oncology Group (ECOG) compared gemcitabine plus bolus 5-FU with gemcitabine alone for patients with advanced pancreatic carcinoma. The trial involved patients with biopsy-proven, advanced carcinoma of the pancreas not amenable to surgical resection. Patients were randomized to receive either gemcitabine alone (1,000 mg/m^2/week) weekly for 3 weeks of every 4 or to receive gemcitabine (1,000 mg/m^2/week) followed by 5-FU (600 mg/m2/week) weekly on the same schedule. The primary end point of the trial was survival, with secondary end points of time to progression and response rate. Of 327 patients enrolled over 18 months, 322 were eligible. Overall, the median survival was 5 months for gemcitabine alone and 7 months for gemcitabine plus 5-FU, which was a not significant difference. Progression-free survival for gemcitabine alone was 2 months, compared with 3 months for gemcitabine plus 5-FU, which on the other hand was a statistical difference. Objective responses were uncommon and were observed in only 6 percent of patients treated with gemcitabine and 7 percent of patients treated with gemcitabine plus 5-FU. Most toxicities were hematologic or gastrointestinal; no significant differences were noted between the two treatment arms. The authors concluded that 5-FU, administered in

conjunction with gemcitabine, did not improve the median survival of patients with advanced pancreatic carcinoma compared with single-agent gemcitabine [158].

> *Summary: There are no indications that the combination of gemcitabine and 5FU is of value in patients with advanced pancreatic cancer.*

Gemcitabine and capecitabine

In a phase III trial compared the efficacy and safety of gemcitabine (Gem) plus capecitabine (GemCap) versus single-agent Gem in advanced/metastatic pancreatic cancer. Patients were randomly assigned to receive GemCap (oral capecitabine 650 mg/m^2 twice daily on days 1 to 14 plus Gem 1,000 mg/m^2 by 30-minute infusion on days 1 and 8 every 3 weeks) or Gem (1,000 mg/m^2 by 30-minute infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks). Patients were stratified according to center, Karnofsky performance score (KPS), presence of pain, and disease extent. A total of 319 patients were enrolled between 2001 and 2004. Median overall survival (OS) time, the primary end point, was 8.4 and 7.2 months in the GemCap and Gem arms, respectively, which was a not statistically significant difference. Post hoc analysis in patients with good KPS (score of 90 to 100) showed a significant prolongation of median overall survival time in the GemCap arm compared with the Gem arm (10 vs 7 months, respectively). The overall frequency of grade 3 or 4 adverse events was similar in each arm. Neutropenia was the most frequent grade 3 or 4 adverse event in both arms. It was concluded that GemCap failed to improve overall survival time at a statistically significant level compared with standard Gem treatment. The safety of GemCap and Gem was similar. In the subgroup of patients with good performance status, median overall survival was, however, improved significantly [159].

Gemcitabine has shown potential synergistic activity with the oral fluoropyrimidine capecitabine in previous phase I/II trials. Based on this background and in order to define the therapeutic potential and tolerance of this combination more precisely, a multicenter phase II trial was initiated prospectively randomizing 83 patients to treatment with biweekly gemcitabine 2,200 mg/m^2 given as a 30 min intravenous infusion on day 1, or the same treatment plus oral capecitabine 2,500 mg/m^2 given from days 1 to 7. In both arms, chemotherapy was administered for a duration of 6 months unless there was prior evidence of progressive disease. The efficacy of the two treatment arms was evaluated according to standard criteria, i.e. objective response, progression-free survival and overall survival, as well as by analysis of clinical benefit response. The overall objective response rate among the 42 patients treated with gemcitabine alone was 14 percent compared with 17 percent among those treated with the combination arm. Similar to response rates, there was no apparent difference between the two groups in terms of median progression-free survival (4 vs 5 months) and median overall survival (8 vs 10 months) in the gemcitabine and combination arm, respectively. Of 61 patients with tumor-related symptoms, who were considered evaluable for clinical benefit response, 10/30 and 15/31 experienced significant palliation in the gemcitabine and combination arm, respectively. Chemotherapy was well tolerated in both arms with only four versus six patients experiencing WHO grade 3 symptoms. Apart from the occurrence of hand-foot syndrome in 10 patients, no major increase in incidence and/or degree of adverse reactions was noted in the combination arm. Despite a somewhat superior clinical benefit response rate, no advantage over single-agent gemcitabine, however, was noted in terms of objective efficacy parameters [160].

To compare clinical benefit response (CBR) and quality of life (QOL) in patients receiving gemcitabine (Gem) plus capecitabine (Cap) versus single-agent Gem for advanced/metastatic pancreatic cancer. Patients were randomly assigned to receive GemCap (oral Cap 650 mg/m^2 twice daily on days 1 through 14 plus Gem 1,000 mg/m^2 in a 30-minute infusion on days 1 and 8 every 3 weeks) or Gem (1,000 mg/m^2 in a 30-minute

infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks) for 24 weeks or until progression. CBR criteria and QOL indicators were assessed over this period. CBR was defined as improvement from baseline for $\geq$ 4 consecutive weeks in pain (pain intensity or analgesic consumption) and Karnofsky performance status, stability in one but improvement in the other, or stability in pain and performance status but improvement in weight. Of 319 patients, 19 percent treated with GemCap and 20 percent treated with Gem experienced a clinical benefit response, with a median duration of 10 and 7 weeks, respectively, which was a significant difference; 54 percent of patients treated with GemCap and 60 percent treated with Gem had no clinical benefit response (remaining patients were not assessable). There was no treatment difference in QOL (n=311). QOL indicators were significantly improving under chemotherapy. These changes differed by the time to failure, with a significant worsening 1 to 2 months before treatment failure. It was concluded that there is no indication of a difference in clinical benefit response or QOL between GemCap and Gem. Regardless of their initial condition, some patients experience an improvement in QOL on chemotherapy, followed by a worsening before treatment failure [161].

Both gemcitabine (GEM) and fluoropyrimidines are valuable treatment for advanced pancreatic cancer. This open-label study was designed to compare the overall survival of patients randomly assigned to GEM alone or GEM plus capecitabine (GEM-CAP). Patients with previously untreated histologically or cytologically proven locally advanced or metastatic carcinoma of the pancreas with a performance status $\leq$ 2 were recruited. Patients were randomly assigned to GEM or GEM-CAP. The primary outcome measure was survival. Between 2002 and 2005, 533 patients were randomly assigned to GEM (n=266) and GEM-CAP (n=267) arms. GEM-CAP significantly improved objective response rate (19 vs 12 %) and progression-free survival (hazard ratio 0.78; 95 % confidence interval, 0.66 to 0.93) and was associated with a trend toward improved overall survival (hazard ratio 0.86; 95 % confidence interval 0.72 to 1.02) compared with GEM alone. This trend for overall survival benefit for GEM-CAP was consistent across different prognostic subgroups according to baseline stratification factors (stage and performance status) and remained after adjusting for these stratification factors. Moreover, the meta-analysis of two additional studies involving 935 patients showed a significant survival benefit in favor of GEM-CAP (hazard ratio, 0.86; 95 % confidence interval 0.75 to 0.98) with no intertrial heterogeneity. It was concluded that on the basis of this trial and the meta-analysis, GEM-CAP should be considered as one of the standard first-line options in locally advanced and metastatic pancreatic cancer [162].

> *Summary: Just like with 5FU, there are little indications that the combination of gemcitabine and capecitabine is of value in patients with advanced pancreatic cancer.* If *there are differences, these are probably clinically very small.*

Gemcitabine and cisplatin

To compare the effectiveness and tolerability of gemcitabine plus cisplatin with single-agent gemcitabine as first-line chemotherapy for locally advanced or metastatic pancreatic cancer patients with advanced adenocarcinoma of the pancreas were randomly assigned to receive either gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2 given on days 1 and 15 of a 4-week cycle (GemCis arm) or gemcitabine alone at a dose of 1,000 mg/m^2 on days 1, 8, and 15 of a 4-week regimen (Gem arm). The primary end point was overall survival; secondary end points were progression-free survival, response rate, safety, and quality of life. One hundred ninety-five patients were enrolled and showed baseline characteristics well balanced between treatment arms. Combination treatment in the GemCis arm was associated with a prolonged median progression-free survival (5 months vs 3 months; hazard ratio, HR, 0.75; p=0.053). Also, median overall survival was superior for patients treated in the GemCis arm as compared with the Gem arm (8 vs 6 months), an advantage which did not, however, reach statistical significance (HR = 0.80). Tumor response rates were comparable between

treatment arms (10 % vs 8 %). The rate of stable disease was, however, significally greater in the combination arm (60 % vs 40 %; p<0.001). Grade 3 to 4 hematologic toxicity did not exceed 15 percent in any treatment arms. This means that median overall survival and progression-free survival were more favorable in the combination arm as compared with gemcitabine alone, although the difference did not attain statistical significance [163].

A multi-center randomized phase III clinical trial was designed to evaluate the efficacy, clinical benefit response (CBR) and toxicity profile of germcitabine (GEM) or GEM plus cisplatin (CDDP) for locally advanced or metastatic pancreatic cancer. From 2000 to 2001, 42 untreated patients were randomized into two groups: Arm A-GEM 20 patients and Arm B-GEM + CDDP 22 patients. Eligibility criteria were: cytologically and pathologically proven pancreatic carcinoma, Karnosky performance status 60-80, age 18-75 years, adequate hematological, renal and liver function, measurable disease, and controllable pain. For Arm A patients, weekly dose of gemcitabine 1 000 mg/m^2/week for 7 times followed by a week rest. Then weekly gemcitabine at the same dose for 3 times every 4 weeks. Arm B patients were given weekly dose of gemcitabine 1 000 mg/m^2/w for 3 times every 4 weeks combined with cisplatin 60 mg/m^2 on D15 for 3 cycles. Thirty-four patients were available for objective response (Arm A 16 and Arm B 18) and 36 (Arm A 16 and Arm B 20) for clinical benefit response evaluation. In Arm A and Arm B, 1 (6 %) and 2 partial responses (11 %), respectively, were observed. Positive clinical benefit response was 88 percent in Arm A and 70 percent in Arm B. The 12-month survival rates of Arm A and B was 31 percent and 11 percent, with median survivals of 273 and 217 days, respectively. The incidence of hematological and non-hematological toxicity of Arm A was lower than that of Arm B without statistical significance. The toxicity ranging from being mild to moderate was manageable [164].

A prospective, randomized Phase III trial was performed to determine whether, compared with gemcitabine (GEM) alone, the addition of cisplatin (CDDP) to GEM was able to improve the time to disease progression and the clinical benefit rate in patients with advanced pancreatic adenocarcinoma. The objective response rate, overall survival rate, and toxicity patterns of patients in the two treatment arms were evaluated as secondary end points. Patients with measurable, locally advanced and/or metastatic pancreatic adenocarcinoma were randomized to receive GEM (Arm A) or a combination of GEM and CDDP (Arm B). In Arm A, a dose of 1000 mg/m^2 gemcitabine per week was administered for 7 consecutive weeks, and, after a 2-week rest, treatment was resumed on days 1, 8, and 15 of a 28-day cycle for 2 cycles. In Arm B, cisplatin was given at a dose of 25 mg/m^2 per week 1 hour before gemcitabine at the same dose that was used in Arm A. On day 22, only gemcitabine was administered. Patients were restaged after the first 7 weeks of therapy and then again after the other 2 cycles. A total of 107 patients entered the trial; 54 patients were randomized to Arm A, and 53 patients were randomized to Arm B. The median time to disease progression was 8 weeks in Arm A and 20 weeks in Arm B; this difference was statistically significant. In Arm A, one complete response and four partial responses were recorded on the basis of an intent-to-treat analysis, with an overall response rate of 9 percent (95 % confidence interval 3-20 %). In Arm B, there were no complete responses, whereas 14 partial responses were achieved, with an overall response rate of 26 percent (95 % CI 15-40 %). This difference in the overall response rates was statistically significant. The tumor growth control rate (i.e., total number of patients who achieved complete responses, partial responses, and stable disease) was 43 percent (95 % CI 29-57 %) in Arm A and 57 percent (95 % CI 42-70%) in Arm B. A clinical benefit was observed in 21 of 43 patients (49 %) in Arm A and in 20 of 38 patients (53 %) in Arm B without any significant difference. The median overall survival was 20 weeks for patients in Arm A and 30 weeks for patients in Arm B, which was a not significant difference. Toxicity was mild in both treatment arms, with no significant differences between the two groups except for the statistically higher incidence of Grade 1-2 asthenia in Arm B. This means that the addition of cisplatin to gemcitabine

significantly improved the median time to disease progression and the overall response rate compared with gemcitabine alone. The clinical benefit rate was similar in both arms [165].

It was explored the efficacy and toxicity of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in a multi-institutional, randomized, phase II study. Patients with metastatic pancreatic cancer were randomly assigned to one of the following four regimens: gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 with cisplatin 50 mg/m^2 on days 1 and 15 (arm A); gemcitabine 1,500 mg/m^2 at a rate of 10 mg/m^2/min on days 1, 8, and 15 (arm B); gemcitabine 1,000 mg/m^2 with docetaxel 40 mg/m^2 on days 1 and 8 (arm C); or gemcitabine 1,000 mg/m with irinotecan 100 mg/m^2 on days 1 and 8 (arm D). Patients were observed for response, toxicity, and survival. Two hundred fifty-nine patients were enrolled onto the study, of whom 245 were eligible and received treatment. Anticipated rates of myelosuppression, fatigue, and expected regimen-specific toxicities were observed. The overall tumor response rates were 12-14 percent, and the median overall survival times were 6 to 7 months among the four regimens. Gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan have similar antitumor activity in metastatic pancreatic cancer. In light of recent negative randomized studies directly comparing several of these regimens with standard gemcitabine, none of these approaches can be recommended for routine use in patients with this disease [166].

Meta-analysis
To compare the therapeutic effects of gemcitabine (GEM) monotherapy with GEM-cisplatin (DDP) combination chemotherapy in patients with advanced stage pancreatic cancer through meta-analysis. MEDLINE and EMBASE searches were supplemented by information from trial registers of randomized controlled trials for GEM-DDP combination chemotherapy and GEM alone in advanced pancreatic cancer. A quantitative meta-analysis using updated information based on inclusion criteria from all available randomized trials was carried out by two reviewers. The primary meta-analysis involved the overall survival (OS), objective remission rate (ORR) and toxicity. The meta-analysis included six randomized trials. There was no significant advantage for the GEM-DDP combination group in 6-month survival rate or clinical benefit rate. There was a marginal significant improvement for the GEM-DDP combination group in ORR (risk difference 6 %). Moreover, there was a significant improvement for the combination group in 6-month TTP/TTF (risk difference 9 %). WHO grade 3-4 toxicity was higher for the GEM-DDP combination group in terms of neutropenia (risk difference 6 %), thrombocytopenia (risk difference 8 %) and vomiting/nausea (risk difference 11 %); none reached significant difference. It was concluded that GEM-DDP combination should not be recommended and GEM monotherapy remains the standard treatment for patients with advanced pancreatic cancer [167].

> *Summary: In the two biggest studies there was a small improvement of overall benefit for the addition of cisplatin to gemcitabine, but due to the significant toxicity the meta-analysis did not recommend the combination.*

Gemcitabine and oxaliplatin

It was conducted a phase III study comparing gemcitabine and oxaliplatin, GemOx, with gemcitabine alone in advanced pancreatic cancer. Patients with advanced pancreatic cancer were stratified according to center, performance status, and type of disease (locally advanced vs metastatic) and randomly assigned to either GemOx (gemcitabine 1 g/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks) or Gem (gemcitabine 1 g/m^2 as a weekly 30-minute infusion). Three hundred twenty-six patients were enrolled; 313 were eligible, and 157 and 156 were allocated to the GemOx and Gem arms, respectively. GemOx was significantly superior to Gem in terms of response rate (27 % vs 17 %), progression-free survival (6 vs 4 months), and clinical benefit

(38 % vs 27 %). Median overall survival for GemOx and Gem was 9 and 7 months, which was a statistically not significant difference. GemOx was well tolerated overall, although a higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14 % for GemOx vs 3 % for Gem), vomiting (9 % for GemOx vs 3 % for Gem), and neurosensory symptoms (19 % for GemOx vs 0 % for Gem). The results confirm the efficacy and safety of gemcitabine combined with oxaliplatin, but the study failed to demonstrate a statistically significant advantage in terms of overall survival compared with gemcitabine alone [168].

The aim of one report was to evaluate the efficacy of gemcitabine combined with a platinum agent compared to single-agent gemcitabine in a pooled analysis of two randomized trials. The French Multidisciplinary Clinical Research Group (GERCOR)/Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) intergroup study comparing gemcitabine plus oxaliplatin to gemcitabine and a German multicenter trial comparing gemcitabine plus cisplatin versus gemcitabine were included in a pooled analysis based on individual patient data. Among 503 evaluable patients, 252 received gemcitabine plus a platinum analog, while 251 patients were treated with gemcitabine alone. For progression-free survival, the pooled univariate analysis indicated a hazard ratio of 0.75 in favour of the Gemcitabine and platinum analog combination. The significant benefit from this combination was greatest in the subgroup of patients with performance status = 0 (hazard ratio 0.64). Also overall survival was significantly superior in patients receiving the combination (hazard ratio 0.81). Again, patients with PS = 0 appeared to have a greater benefit from treatment intensification (hazard ratio 0.72). The authors concluded that the pooled analysis of the GERCOR/GISCAD intergroup study and the German multicenter study indicates that the combination of gemcitabine with a platinum analog such as oxaliplatin or cisplatin significantly improves progression-free survival and overall survival as compared to single-agent gemcitabine in advanced pancreatic cancer. The benefit seems to prevail in patients with a good performance status [169].

Single-agent gemcitabine (GEM) is standard treatment of metastatic pancreatic cancer. Fixed-dose rate (FDR) GEM and GEM plus oxaliplatin have shown promise in early clinical trials. One trial was designed to compare overall survival of standard weekly GEM 1,000 mg/m^2/30 minutes versus GEM FDR 1,500 mg/m^2/150 minutes or GEM 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days (GEMOX). The trial included patients with metastatic or locally advanced pancreatic cancer, normal organ function, and performance status of 0 to 2. The study was designed to detect a 33 percent difference in median survival (hazard ratio $\leq$ 0.75 for either of the experimental arms) with 81 percent power while maintaining a significance level of 2.5 percent in a two-sided test for each of the two primary comparisons. Eight hundred thirty-two patients were enrolled. The median survival and 1-year survival were 5 months (95 % confidence interval 5 to 6) and 16 percent for GEM, 6 months (95 % confidence interval 5.4 to 6.9), and 21 percent for GEM FDR (hazard ratio 0.83), and 5 months (95 % confidence interval 5 to 7) and 21 percent for GEMOX (hazard ratio 0.88). Neither of these differences met the prespecified criteria for significance. Survival was 9 months for patients with locally advanced disease, and 5 months for those with metastatic disease. Grade 3/4 neutropenia and thrombocytopenia were greatest with GEM FDR. GEMOX caused higher rates of nausea, vomiting, and neuropathy. It was concluded that neither GEM FDR nor GEMOX resulted in substantially improved survival or symptom benefit over standard GEM in patients with advanced pancreatic cancer [170].

Summary: the combination of gemcitabine with a platinum analog such as oxaliplatin or cisplatin improves progression-free survival and overall survival as compared to single agent gemcitabine in advanced pancreatic cancer, but is toxic.

Gemcitabine and capecitabine or oxaliplatin

To compare the efficacy and safety of three different chemotherapy doublets in the treatment of advanced pancreatic cancer a total of 190 patients were randomly assigned to receive capecitabine 1000 mg/m^2 twice daily on days 1-14 plus oxaliplatin 130 mg/m^2 on day 1 (CapOx), capecitabine 825 mg/m^2 twice daily on days 1-14 plus gemcitabine 1000 mg/m^2 on days 1 and 8 (CapGem) or gemcitabine 1000 mg/m^2 on days 1 and 8 plus oxaliplatin 130 mg/m^2 on day 8 (mGemOx). Treatment cycles were repeated every three weeks. The primary end point was progression-free survival (PFS) rate at 3 months; secondary end points included objective response rate, carbohydrate antigen 19-9 response, clinical benefit response, overall survival and toxicity. The PFS rate after 3 months was 51 percent in the CapOx arm, 64 percent in the CapGem arm and 60 percent in the mGemOx arm. Median PFS was estimated with 4 months, 6 months and 4 months, respectively, which was statistically not significant differences. Corresponding median survival times were: 8 months (CapOx), 9 months (CapGem) and 7 months (mGemOx), which neither was a significant difference. Grade 3/4 hematological toxicities were more frequent in the two Gem-containing arms; grade 3/4 non-hematological toxicity rates did not exceed 15 percent in any arm. CapOx, CapGem and mGemOx have similar clinical efficacy in advanced pancreatic cancer. Each regimen has a distinct but manageable tolerability profile [171].

> *Summary: Combinations of gemcitabine with capecitabine or oxaliplatin had the same effects.*

Gemcitabine and docetaxcel

It was investigated the efficacy and toxicity of docetaxel plus gemcitabine or docetaxel plus cisplatin for advanced pancreatic carcinoma. Chemotherapy-naive patients with measurable disease and WHO performance status less than 2 were randomly assigned to receive 21-day cycles of gemcitabine 800 mg/m^2 on days 1 and 8 plus docetaxel 85 mg/m^2 on day 8 (arm A) or docetaxel 75 mg/m^2 on day 1 plus cisplatin 75 mg/m^2 on day 1 (arm B). Primary end points were tumor response and rate of febrile neutropenia grade. Of 96 randomly assigned patients (49 patients in arm A and 47 patients in arm B), 70 patients were analyzed for response (36 in arm A and 34 in arm B) and 89 patients were analyzed for safety (45 in arm A and 44 in arm B). Confirmed responses were observed in 19 percent (95 % CI, 8 % to 36 %) of patients in arm A and 24 percent (95 % CI, 11 % to 41 %) in arm B. In arm A, the median progression-free survival was 4 months (95 % CI, 3 to 5 months), median survival was 7 months (95 % CI, 6 to 11 months), and 1-year survival was 30 percent. In arm B, the median progression-free survival was 3 months (95 % CI, 3 to 5 months), median survival was 7 months (95 % CI, 5 to 9 months), and 1-year survival was 16 percent. Febrile neutropenia occurred in 9 percent and 16 percent of patients in arms A and B, respectively [172].

> *Summary: The combination of gemcitabine and docetaxel cannot be recommended.*

Gemcitabine and irinotecan

The purpose of a study was to determine the response rate and median and overall survival of gemcitabine as monotherapy versus gemcitabine plus irinotecan in advanced or metastatic pancreatic cancer. Patients with histologically or cytologically confirmed adenocarcinoma who were chemotherapy and radiotherapy naive were enrolled. Patients were centrally randomised at a one-to-one ratio to receive either gemcitabine monotherapy (900 mg m^2 on days 1, 8 and 15 every 4 weeks (arm G), or gemcitabine (days 1 and 8) plus irinotecan (300 mg m^2 on day 8) (arm IG), repeated every 3 weeks. The total number of cycles administered was 255 in the IG arm and 245 in the G arm; the median number of

cycles was 3. In all, 145 patients (71 in arm IG and 74 in arm G) were enrolled; 60 and 70 patients from arms IG and G, respectively, were evaluable. A complete clinical response was achieved in three (4 %) arm G patients; nine (15 %) patients in arm IG and four (6 %) in arm G achieved a partial response. The overall response rate was: arm IG 15 percent and arm G 10 percent, which was a not significant difference. The median time to tumour progression was 2.8 months and 2.9 months and median survival time was 6.4 and 6.5 months for the IG and G arms, respectively. One-year survival was 24 percent for the IG arm and 22 percent for the G arm. This means that no statistically significant difference was observed comparing gemcitabine monotherapy versus gemcitabine plus irinotecan in the treatment of advanced pancreatic cancer, with respect to overall and 1-year survival [173].

A phase III, randomized, open-label, multicenter study compared the overall survival associated with irinotecan plus gemcitabine (IRINOGEM) versus gemcitabine monotherapy (GEM) in patients with chemotherapy-naive, locally advanced or metastatic pancreatic cancer. IRINOGEM patients received starting doses of gemcitabine 1,000 mg/m^2 and irinotecan 100 mg/m^2 given weekly for 2 weeks every 3-week cycle. GEM patients received gemcitabine 1,000 mg/m^2 weekly for 7 of 8 weeks (induction) and then weekly for 3 of 4 weeks. The primary end point of the trial was survival. Secondary end points included tumor response, time to tumor progression, changes in CA 19-9, and safety. In each arm, 180 randomly assigned patients comprised the intent-to-treat population evaluated for efficacy; 173 IRINOGEM and 169 GEM patients were treated. Median survival times were 6 months for IRINOGEM (95 % CI, 5 to 8 months) and 7 months for GEM (95 % CI, 5 to 8 months), which was a not significant difference. Tumor response rates were 16 % (95 % CI, 11 % to 22 %) for IRINOGEM and 4 percent (95 % CI, 2 % to 9 %) for GEM, which was a statistically significant difference. Median time to tumor progression was 4 months for IRINOGEM versus 3 months for GEM (not significant differente). However, subset analyses in patients with locally advanced disease suggested a time to tumor progression advantage with IRINOGEM versus GEM (median, 8 vs 4 months). CA 19-9 progression was positively correlated with tumor progression. The incidence of grade 3 diarrhea was higher in the IRINOGEM group but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were simila [174].

> *Summary: This means that the larger study showed a difference that could not be found in the smaller – which is unusual. However, there was a tendency for some positive effect also in the smaller study. The doses are not totally comparable, with the exception that in the group that had a positive effect the patients only got 2/3 of the irinotecan that was given to the patients that had no effect. Together, the studies indicate that irinotecan may be of benefit together with gemcitabine – or at least that it should be considered for further studies.*

Gemcitabine and uracil/tegafur

Patients with invasive ductal pancreatic cancer who underwent radical surgery were enrolled and assigned to receive uracil/tegafur (UFT) and GEM together (GU) or GEM alone (G). GEM was administrated at a dosage of 1 g/m^2 intravenously weekly 3 of 4 weeks and UFT at a dosage of 200 mg/day orally continuously. Eligibility included resection status 0 or 1, and no previous chemo- or/and radiation therapy. The primary endpoint was disease-free survival (DFS), and secondary endpoints included overall survival (OS) and toxicity. Between 2002 and 2005, 100 patients were randomized into the 2 arms of the trial (50 patients to GU and 50 to G). One patient in the G group was found to be ineligible. Baseline characteristics were well balanced between the two groups. With a median observation period of 21 months, the 1- and 3-year DFS rates were 50 percent and 18 percent in the GU group and 49 percent and 22 percent in the G group, respectively. The median OS was 21 months in the GU group and 30 months in the G group. Toxicity was minor and acceptable, less than grade 4 in both groups. Postoperative gemcitabine-based adjuvant chemotherapy was safe and well

tolerated. However, addition of UFT with gemcitabine did not improve disease-free survival as compared with gemcitabine alone. Further clinical trial resources for adjuvant chemotherapy should address other combinations and novel agents [175].

Summary: The combination of gemcitabine and uracil/tegafur cannot be recommended.

Gemcitabine, cisplatin and cetuximab

Preclinical data have suggested a synergistic effect of cetuximab combined with gemcitabine and cisplatin and clinical data have shown a substantial improvement in response and survival when gemcitabine is combined with a platinum analogue compared with gemcitabine alone. The aim of one study was to assess the activity and feasibility of a combination of cetuximab with gemcitabine and cisplatin compared with use of gemcitabine and cisplatin alone for the treatment of advanced pancreatic cancer. In a multicentre, randomised phase II trial, 84 patients with advanced pancreatic cancer were randomly assigned to either 250 mg/m^2 cetuximab weekly, after a loading dose of 400 mg/m^2, plus 1000 mg/m^2 gemcitabine and 35 mg/m^2 cisplatin on days 1 and 8 of a 21-day cycle or to the same chemotherapeutic regimen without cetuximab. The primary endpoint was objective response (defined as the proportion of patients whose best response was either partial response or complete response). Secondary endpoints included disease control (defined as the proportion of patients whose best response was either partial response, complete response, or stable disease), progression-free survival, and overall survival. All assessments of response at each site were done blindly by a local experienced radiologist who was not directly involved in the trial. Responses were measured according to an intention-to-treat analysis. Twenty-nine men and 13 women were randomly assigned to cetuximab plus gemcitabine and cisplatin (median age 61 years) and 22 men and 20 women were randomly assigned to gemcitabine and cisplatin. Seven of 40 (18 %) patients had an objective response in the cetuximab group (95 % confidence interval 7 to 33) and five of 41 (12 %) patients had an objective response in the non-cetuximab group (95 % confidence interval 4 to 26). No significant difference was noted between the groups both for objective response (5 % higher in the cetuximab group or for disease control (4 % higher in the non-cetuximab group). Overall median follow-up was 12 months (range 3-19). No significant differences between the groups were noted in median progression-free survival or in median overall survival: median progression-free survival was 3 months (95 % confidence interval 2 to 5) in the cetuximab group and 4 months (95 % confidence interval 3 to 5) in the non-cetuximab group; median overall survival was 8 months (5-9) and 8 months (5-15), respectively. Thirty-three patients from both groups had at least one grade 3-4 toxic effect. The addition of cetuximab to a combination of gemcitabine and cisplatin does not increase response or survival for patients with advanced pancreatic cancer. Although toxic effects were not increased by cetuximab, this combination should not be further assessed in phase III trials [176].

Summary: The addition of cetuximab to a combination of gemcitabine and cisplatin does not increase response or survival

Gemcitabine and PEFG

It was assessed whether a four-drug regimen could improve 4 month progression-free survival compared with gemcitabine alone. In a randomised multicentre phase III trial, 52 patients were randomly assigned to 40 mg/m^2 cisplatin and 40 mg/m^2 epirubicin both given on day 1, 600 mg/m^2 gemcitabine given intravenously over 1 h on days 1 and 8, and 200 mg/m^2 fluorouracil a day given by continuous infusion on days 1-28 of a 4-week cycle (PEFG regimen), and 47 were assigned to 1000 mg/m^2 gemcitabine given intravenously over 30 min once a week for 7 of 8 consecutive weeks in cycle 1 and for 3 of 4 weeks thereafter. The primary endpoint was 4-month progression-free survival. Secondary endpoints were overall

survival, objective response, safety, and quality of life. Fifty-five patients assigned PEFG and 46 assigned gemcitabine alone had disease progression. Fourty-nine patients in the PEFG group and 46 in the gemcitabine group died from progressive disease. More patients allocated PEFG than gemcitabine alone were alive without progressive disease at 4 months (60 %; 95% CI 46-72 % vs 28 %; 17-42; hazard ratio 0.46; 0.26-0.79). 1-year overall survival in the PEFG group was 39 % (25-52) and in the gemcitabine group was 21 percent (10-33 %; HR 0.68). More patients assigned PEFG showed disease response than did those assigned gemcitabine (39 % vs 9 %, a significant difference). Significantly more patients in the PEFG group had grade 3-4 neutropenia and thrombocytopenia than in the gemcitabine group [177].

> *Summary: There were positive effects of the PEFG combination, but to the cost of significant toxicity.*

Gemcitabine and erlotinib plus bevacizumab

The addition of erlotinib to gemcitabine shows a small but significant improvement in overall survival (OS) versus gemcitabine alone. Phase II results for bevacizumab plus gemcitabine provided the rationale for a phase III trial of gemcitabine-erlotinib plus bevacizumab or placebo. Patients with metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine (1,000 mg/m/week), erlotinib (100 mg/day), and bevacizumab (5 mg/kg every 2 weeks) or gemcitabine, erlotinib, and placebo in this double-blind, phase III trial. Primary end point was OS; secondary end points included progression-free survival (PFS), disease control rate, and safety. A total of 301 patients were randomly assigned to the placebo group and 306 to the bevacizumab group. Median OS was 7 and 6 months in the bevacizumab and placebo arms, respectively (hazard ratio 0.89; 95 % confidence interval 0.74 to 1.07); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved progression-free survival (hazard ratio 0.73; 95 % confidence interval 0.61 to 0.86). Treatment with bevacizumab plus gemcitabine-erlotinib was well tolerated: safety data did not differ from previously described safety profiles for individual drugs. It was concluded that the primary objective was not met. The addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS in patients with metastatic pancreatic cancer. Progression-free survival, however, was significantly longer in the bevacizumab group compared with placebo. No unexpected safety events were observed from adding bevacizumab to gemcitabine-erlotinib [178].

> *Summary: The addition of bevacizumab to gemcitabine-erlotinib was useless (but expensive)*

Gemcitabine and vascular endothelial growth factor receptors

Axitinib (AG-013736) is a potent and selective oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, which have an important role in pancreatic cancer. The aim of one study was to assess the safety and efficacy of gemcitabine plus axitinib versus gemcitabine alone. In 2006 103 patients with unresectable, locally advanced, or metastatic pancreatic cancer were randomly assigned in a two to one ratio to receive gemcitabine (1000 mg/m^2) plus axitinib 5 mg twice daily (n=69) or gemcitabine (1000 mg/m^2) alone (n=34) by a centralised registration system. The primary endpoint was overall survival. Analyses were done by intention to treat. All randomised patients were included in the efficacy analyses. Median overall survival was longer with gemcitabine plus axitinib than with gemcitabine alone (7 months with 95 % confidence interval 5 to 10 months vs 6 months with 95 % confidence interval 4 to 9 months). The hazard ratio for survival with gemcitabine plus axitinib versus with gemcitabine alone, adjusted for stratification factors, was 0.71. The most common grade 3 or worse adverse events were fatigue (22 % of patients in the gemcitabine plus axitinib

group vs 3 % in the gemcitabine alone group), abdominal pain (12 % vs 16 %), and asthenia (12 % vs 3 %). It was concluded that gemcitabine plus axitinib showed a similar safety profile to gemcitabine alone; there was a small, non-statistically significant gain in overall survival with the combination with vascular endothelial growth factor receptors [179].

Summary: The addition of a vascular endothelial growth factor receptors to gemcitabine was useless (but probably expensive).

Gemcitabine and other anti-angiogenic agents

Anti-angiogenic treatment is believed to have at least cystostatic effects in highly vascularized tumours like pancreatic cancer. Now the angiogenesis inhibitor Cilengitide and gemcitabine were compared with gemcitabine alone in patients with advanced unresectable pancreatic cancer in a multi-national, open-label, controlled, randomized, parallel-group, phase II pilot study in 20 centers in 7 countries. Cilengitide was administered at 600 mg/m^2 twice weekly for 4 weeks per cycle and gemcitabine at 1000 mg/m^2 for 3 weeks followed by a week of rest per cycle. The planned treatment period was 6 four-week cycles. The primary endpoint of the study was overall survival and the secondary endpoints were progression-free survival (PFS), response rate, quality of life (QoL), effects on biological markers of disease (CA 19.9) and angiogenesis (vascular endothelial growth factor and basic fibroblast growth factor), and safety. An ancillary study investigated the pharmacokinetics of both drugs in a subset of patients. Eighty-nine patients were randomized. The median overall survival was 6.7 months for Cilengitide and gemcitabine and 7.7 months for gemcitabine alone. The median PFS times were 3.6 months and 3.8 months, respectively. The overall response rates were 17 percent and 14 percent, and the tumor growth control rates were 54 percent and 56 percent, respectively. Changes in the levels of CA 19.9 went in line with the clinical course of the disease, but no apparent relationships were seen with the biological markers of angiogenesis. QoL and safety evaluations were comparable between treatment groups. Pharmacokinetic studies showed no influence of gemcitabine on the pharmacokinetic parameters of Cilengitide and vice versa. This means that there were no clinically important differences observed regarding efficacy, safety and quality of life between the groups. The observations lay in the range of other clinical studies in this setting [180].

Comment: Despite a thrilling theoretically and basic science background it is still not shown clinically that anti-angiogenic treatment is of value in pancreatic cancer.

Gemcitabine and infliximab

To evaluate the safety and efficacy of infliximab administered with gemcitabine to treat cancer cachexia and to explore a functional measure of clinical benefit, investigators involved in this multicenter, phase II, placebo-controlled study randomized 89 patients with stage II-IV pancreatic cancer and cachexia to receive either placebo or 3 mg/ kg or 5 mg/kg of infliximab at weeks 0, 2, and 4 and then every 4 weeks to week 24; patients also received 1,000 mg/m2 of gemcitabine weekly from weeks 0-6 and then for 3 of every 4 weeks until their disease progressed. The primary endpoint was change in lean body mass (LBM) at 8 weeks from baseline; major secondary endpoints included overall survival, progression-free survival, Karnofsky performance status, and 6-minute walk test distance. In addition, quality of life was measured. The mean change in LBM at 8 weeks was +0.4 kg for patients receiving placebo, +0.3 kg for those receiving 3 mg/kg of infliximab, and +1.7 kg for those receiving 5 mg/kg of infliximab. No statistically significant differences in LBM or secondary endpoints were observed among the groups. Safety findings were similar in all groups. Adding infliximab to gemcitabine to treat cachexia in advanced pancreatic cancer patients

was not associated with statistically significant differences in safety or efficacy when compared with placebo [181].

Summary: The addition of infliximab to gemcitabine was useless (but expensive)

Gemcitabine and HER1/EGFR

Pancreatic tumors often overexpress human epidermal growth factor receptor type 1 (HER1/EGFR) and this is associated with a worse prognosis. It was studied the effects of adding the HER1/EGFR-targeted agent erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer. Patients were randomly assigned 1:1 to receive standard gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo in a double-blind, international phase III trial. The primary end point was overall survival. A total of 569 patients were randomly assigned. Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/gemcitabine arm with a hazard ratio (HR) of 0.82 (95 % confidence interval, 0.69 to 0.99; p=038, adjusted for stratification factors; median 6.2 months vs 5.9 months). One-year survival was also greater with erlotinib plus gemcitabine (23 % vs 17 %; p=0.023). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95 % CI, 0.64 to 0.92; p=0.004). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization. There was a higher incidence of some adverse events with erlotinib plus gemcitabine, but most were grade 1 or 2 [182].

Comment: Even though this study from a statistical point of view shows significant differences between groups it must be underline that the differences are small. For example the overall survival increased 0.3 months, i.e. around 1½ weeks. These benefits must be weighted against adverse events and increased costs.

Gemcitabine and farnesyltransferase

To determine whether addition of the farnesyltransferase inhibitor tipifarnib (Zarnestra, R115777) to standard gemcitabine therapy improves overall survival in advanced pancreatic cancer a randomized, double-blind, placebo-controlled study compared gemcitabine + tipifarnib versus gemcitabine + placebo in patients with advanced pancreatic adenocarcinoma previously untreated with systemic therapy. Tipifarnib was given at 200 mg bid orally continuously; gemcitabine was given at 1,000 mg/m^2 intravenously weekly x 7 for 8 weeks, then weekly x 3 every 4 weeks. The primary end point was overall survival; secondary end points included 6-month and 1-year survival rates, progression-free survival, response rate, safety, and quality of life. Six hundred eighty-eight patients were enrolled. Baseline characteristics were well balanced between the two treatment arms. No statistically significant differences in survival parameters were observed. The median overall survival for the experimental arm was 193 versus 182 days for the control arm; 6-month and 1-year survival rates were 53 percent and 27 percent versus 49 percent and 24 percent for the control arm, respectively; median progression-free survival was 112 versus 109 days for the control arm. Ten drug-related deaths were reported for the experimental arm and seven for the control arm. Neutropenia and thrombocytopenia grade $\geq$3 were observed in 40 and 15 percent in the experimental arm versus 30 and 12 percent in the control arm. Incidences of nonhematologic adverse events were similar in two groups. This means that the combination of gemcitabine and tipifarnib does not prolong overall survival in advanced pancreatic cancer compared with single-agent gemcitabine [183].

Summary: The addition of farnesyltransferase to gemcitabine was not useful.

Gemcitabine and pemetrexed

A randomized phase III study compared the overall survival of pemetrexed plus gemcitabine (PG) versus standard gemcitabine (G) in patients with advanced pancreatic cancer. Patients with unresectable locally advanced or metastatic pancreatic cancer and no prior systemic therapy (including 5-fluorouracil as a radiosensitizer) were randomized to receive either 1,250 mg/m^2 gemcitabine on days 1 and 8 plus pemetrexed 500 mg/m^2 after gemcitabine on day 8 (PG arm) of each 21-day cycle, or gemcitabine 1,000 mg/m^2 on days 1, 8 and 15 of each 28-day cycle (G arm). Five hundred and sixty-five patients with well-balanced baseline characteristics were randomly assigned (283 PG, 282 G). Overall survival was not improved in the PG arm (6 months) compared with the G arm (6 months). Progression-free survival (3.9 versus 3.3 months) and time to treatment failure (3 versus 2 months) results were similar. Tumor response rate (15 % vs 7 %) was, however, significantly better in the PG arm. Grade 3 or 4 neutropenia (45 % vs 13 %), thrombocytopenia (18 % vs 6 %), anemia (14 % vs 3 %), febrile neutropenia (10 % vs 0.4 %) and fatigue (15 % versus 7 %) were significantly more common on the PG arm. Four treatment-related deaths occurred on the PG arm and none in the G arm [184].

> *Summary: The addition of pemetrexed to gemcitabine was not useful.*

Gemcitabine and topoisomerase inhibitors

Exatecan mesylate is a hexacyclic, water-soluble, topoisomerase-1 inhibitor. Exatecan has single-agent and combination activity with gemcitabine in advanced pancreatic cancer. A multicenter, randomized, phase III trial comparing exatecan plus gemcitabine versus gemcitabine alone in advanced pancreatic cancer was conducted. Eligibility criteria included Karnofsky performance status $\geq$ 60 percent, locally advanced or metastatic pancreatic adenocarcinoma, and no prior chemotherapy. Radiation alone for locally advanced disease was permitted. Patients were randomly assigned on a 1:1 basis. For the exatecan plus gemcitabine arm, exatecan 2.0 mg/m^2 and gemcitabine 1,000 mg/m^2 were administered on days 1 and 8, every 3 weeks. Gemcitabine alone was dosed at 1,000 mg/m^2 up to 7 weeks in the first cycle, then once a week for the first 3 weeks of a 4-week cycle. Tumor assessment was performed every 6 weeks. The primary end point was overall survival. An intent-to-treat analysis was used. From 2001 to 2003, 349 patients were randomly assigned, 175 to exatecan plus gemcitabine and 174 to gemcitabine alone. Twenty-four patients (7 %) were not treated. The median survival time was 7 months for exatecan plus gemcitabine and 6 months for gemcitabine alone (a not significant difference). One complete response (CR < 1%) and 11 partial responses (PRs 6 %) were observed in the exatecan plus gemcitabine treatment group, and one CR (< 1 %) and eight PRs (5 %) were observed in the gemcitabine-alone group. Grade 3 and 4 toxicities were higher for the exatecan plus gemcitabine arm versus the gemcitabine alone arm; neutropenia (30 % vs 15 %) and thrombocytopenia (15 % vs 4 %). This means that exatecan plus gemcitabine was not superior to gemcitabine alone with respect to overall survival in the first-line treatment of advanced pancreatic cancer [185].

> *Summary: The addition of a topomerase inhibitor to gemcitabine was not useful.*

Gemcitabine and proteasome inhibitor

PS-341 is a proteasome inhibitor with preclinical activity in pancreatic cancer tumor models and synergistic activity with gemcitabine. This randomized phase II study determined the tumor response rate (RR) for PS-341 alone and the 6-month survival and RR for the combination of gemcitabine and PS-341 in patients with metastatic pancreatic

adenocarcinoma. Patients were randomized to receive 3-week cycles of either arm A: PS-341 1.5 mg/m^2 i.v. bolus (over 3-5 s) on days 1, 4, 8 and 11 or arm B: PS-341 1.0 mg/m^2 (same as arm A otherwise) plus gemcitabine 1,000 mg/m^2 i.v. on days 1 and 8. Patients progressing on arm A were allowed to receive arm B treatment. To arm A 42 evaluable patients were enrolled with a confirmed response rate of 0 percent (95 % CI 0 % to 8 %), median survival of 3 months (95 % CI 2.0-3.3), and median time to progression (TTP) of 1.2 months (95 % CI 1.1-1.3). Twelve of 43 evaluable patients (28 %) experienced at least one grade 4+ adverse effect. In arm B 39 evaluable patients yielded a 6-month survival rate of 41 percent (95% CI 30 % to 67 %), median survival of 5 months (95 % CI 2.4-7.4), median time to progression of 2.4 months (9 5% CI 1.5-3.1), and confirmed response rate of 10 percent (4 partial responses but 0 complete responses; 95 % CI 3 % to 24 %). Eleven of 43 evaluable patients (26 %) experienced at least one grade 4+ adverse effect [186].

Summary: The addition of proteasome inhibitor to gemcitabine was not useful.

Gemcitabine and histone deacetylase inhibitor

An oral histone deacetylase inhibitor, CI-994, has antineoplastic activity and synergism with gemcitabine preclinically. A randomized phase II trial explored whether CI-994 plus gemcitabine improves overall survival, objective response, duration of response, time to treatment failure and change in quality of life (QoL) or pain compared with gemcitabine alone. A total of 174 patients received CI-994 and gemcitabine (CI-994 6 mg/m^2/day days 1-21 plus gemcitabine 1000 mg/m^2/day 1, 8 and 15 each 28-day cycle) or placebo plus gemcitabine 1000 mg/m^2 days 1, 8 and 15 of each 28-day cycle days 1-21. Median survival was 194 days for the CI-994 and gemcitabine group versus 214 days for the placebo and gemcitabine group, which was a not statistically significant difference. The objective response rate was 12 percent versus 14 percent with when investigator-assessed and 1 percent versus 6 percent, respectively, when assessed centrally. Time to treatment failure did not differ between the two arms. Quality of life scores at 2 months were worse with the combination than with plain gemcitabine. Pain response rates were similar between the two groups. There was no difference in incidence of neutropenia and thrombocytopenia [187].

Summary: The addition of histone deacetylase inhibitor to gemcitabine was not useful.

Gemcitabine and a leukotriene B4 receptor antagonist

LY293111 (LY) is a novel oral anticancer agent with leukotriene B4 receptor antagonist and peroxisome proliferator-activated receptor gamma agonist properties, producing promising results alone and in combination with gemcitabine in pancreatic cancer xenograft models. A phase I study proved that the combination (gemcitabine plus LY) is safe and well tolerated. Chemotherapy-naive patients with histologically confirmed locally advanced or metastatic adenocarcinoma of the pancreas were randomly assigned to gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle and continuously administered LY 600 mg twice daily or gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle and daily oral placebo. Arms were balanced for Eastern Cooperative Oncology Group performance status and disease stage. The primary end point was 6-month survival; secondary objectives include response rate, progression-free survival, and overall survival. Six-month survival was not different between groups; progression-free survival and response rate were not different. LY did not increase grades 3-4 hematologic toxicities, but was associated with a trend toward more, grades 3-4 diarrhea. These results do not demonstrate any benefit to adding LY to gemcitabine in unpretreated patients with advanced pancreatic carcinoma [188].

Summary: The addition of a leukotriene B4 receptor antagonist to gemcitabine was not useful.

Meta-analyses

Single-agent gemcitabine (GEM) is a standard treatment for advanced and metastatic pancreatic cancer. One study examinesdthe question whether GEM-based combination chemotherapy can further improve treatment efficacy. A meta-analysis was performed to evaluate randomized trials comparing GEM versus GEM+X (X = cytotoxic agent). Fifteen trials including 4465 patients were eligible for an analysis of overall survival, the primary end-point of this investigation. The meta-analysis revealed a significant survival benefit for GEM+X with a pooled hazard ratio of 0.91 (95 % confidence interval 0.85 to 0.97). The analysis of platinum-based combinations indicated a hazard ratio of 0.85 (95 % confidence interval 0.76 to 0.96), while for fluoropyrimidine-based combinations the hazard ratio was 0.90 (95 % confidence interval 0.81 to 0.99), whih both was statistically significant results. No risk reduction was observed in the group of trials combining GEM with irinotecan, exatecan or pemetrexed (hazard ratio 0.99). A meta-analysis of the trials with adequate information on baseline performance status was performed in five trials with 1682 patients. This analysis indicated that patients with a good performance status had a significant survival benefit when receiving combination chemotherapy (hazard ratio 0.76; 95 % confidence interval 0.67 to 0.87). By contrast, application of combination chemotherapy to patients with an initially poor performance status appeared to be ineffective (hazard ratio1.08; 95 % confidence interval 0.90 to 1.29) It was concluded that the meta-analysis of randomized trials indicated a significant survival benefit when GEM was either combined with platinum analogs or fluoropyrimidines. Based on a preliminary subgroup analysis (representing 38 % of all patients included in this meta-analysis), pancreatic cancer patients with a good performance status appear to benefit from GEM-based cytotoxic combinations, whereas patients with a poor performance status seem to have no survival benefit from combination chemotherapy [189].

To evaluate the impact on overall survival at 6, 12 and 18 months of gemcitabine-based doublets compared with gemcitabine alone in patients with advanced and metastatic pancreatic cancer. It was conducted a systematic review and meta-analysis of published data on the use of gemcitabine-based doublets compared with gemcitabine alone in chemotherapy-naive patients with advanced and metastatic pancreatic cancer treated in randomised controlled phase II-III trials with overall survival as the principal or secondary endpoint. To this end, a literature search was performed using Cochrane methodology. The relative risks with 95 percent confidence intervals were estimated based on adjusted number of deaths and patients at risk according to the extent of follow-up and censoring. Twenty-three randomised clinical trials including 5886 patients met the inclusion criteria. In these trials, 2932 patients were randomly assigned to receive gemcitabine-based doublets and 2954 patients to receive gemcitabine alone. Gemcitabine-based doublets were associated with small but significant reductions in the risk of death at 6, 12 and 18 months of 8 percent (95 % confidence interval 3 to 13), 4 percent (95 % confidence interval 2 to 7) and 3 percent (95 % confidence interval 1 to 5), respectively. No heterogeneity between studies was observed. Subgroup analyses showed an overall survival benefit for gemcitabine-based doublets in clinical trials testing the same planned dose intensity of gemcitabine in comparative arms, using platinum salt-based protocols and with survival as the primary endpoint. It was concluded that this meta-analysis of data obtained from randomised controlled phase II-III trials of patients with advanced pancreatic cancer showed a small but significant improvement in overall survival for patients receiving gemcitabine-based doublets compared with gemcitabine alone [190].

All prospective, randomized, phase III trials that compared single-agent gemcitabine with gemcitabine-based combinations were considered eligible for the current analysis. A literature-based meta-analysis was performed, event-based relative risk ratios with 95 %

confidence intervals were derived through both a fixed-effect model approach and a random-effect model approach, and overall survival was explored as the primary endpoint. To estimate the magnitude of the eventual benefit, absolute differences and the number of patients needed to treat (NNT) for 1 patient to benefit were calculated. A sensitivity analysis for overall survival was performed according to the type of agent used in combination with gemcitabine. Twenty trials that involved 6,296 patients were identified. No significant differences in the primary endpoint were observed in the overall population or in the sensitivity analysis. Conversely, a significant advantage was evident with regard to both progression-free survival (PFS) and the overall response rate (ORR) in the overall population, with an absolute benefit of 2.6 percent (NTT 39 patients) and 3.0 percent (NNT 33 patients). Platinum combinations led to the greatest absolute benefits for PFS and ORR compared with single-agent gemcitabine (10 % and 6.5 %, respectively), but this did not result in an overall survival benefit. Improvement in PFS, but not in the ORR, was correlated with an improvement in OS. It was concluded single-agent gemcitabine remains the standard of care for patients with advanced pancreatic cancer. However, platinum/gemcitabine combinations appeared to improve PFS and the ORR and, thus, may be considered in selected patients [191].

The aim of one meta-analysis was to examine the different therapeutic approaches, and the comparisons examined were as follows: chemotherapy versus best supportive care; fluorouracil (FU) versus FU combination chemotherapy; gemcitabine versus FU; and gemcitabine versus gemcitabine combination chemotherapy. Relevant trials were identified by searching databases, trial registers, and conference proceedings. The primary end point was overall survival. One hundred thirteen randomized controlled trials were identified, of which 51 trials involving 9970 patients met the inclusion criteria. Chemotherapy improved survival compared with best supportive care (hazard ratio 0.64; 95 % confidence interval 0.42 to 0.98). FU-based combination chemotherapy did not result in better overall survival compared with FU alone (hazard ratio 0.94; 95 % confidence interval 0.82 to 1.08). There was insufficient evidence of a survival difference between gemcitabine and FU, but the wide CI includes clinically important differences in both directions, making a clear conclusion difficult (hazard ratio 0.75; 95 % confidence interval 0.42 to 1.31). Survival was improved after gemcitabine combination chemotherapy compared with gemcitabine alone (hazard ratio 0.91; 95 % confidence interval 0.85 to 0.97). It was concluded that there was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone. This supports the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer [192].

To compare gemcitabine-based combination therapy and gemcitabine (GEM) alone in patients with advanced pancreatic cancer through meta-analysis. MEDLINE and EMBASE searches were supplemented by information from trial registers of randomized controlled trials for GEM-based combination therapy and GEM alone for advanced pancreatic cancer. A quantitative meta-analysis was carried out by two reviewers based on the inclusion criteria from all available randomized controlled trials. The meta-analysis involved overall survival (OS), objective remission rate (ORR), clinical benefit rate (CBR), time to progress/progress free survival (TTP/PFS) and toxicity. The meta-analysis included 22 randomized trials. There was significant improvement in the GEM combination group with regard to the 6-months survival rate (RD 0.04, 95 % confidence interval 0.01 to 0.06), 1-year survival rate (RD 0.03; 95 % confidence interval 0.01 to 0.05), objective remission rate (RD 0.04; 95 % confidence interval 0.01 to 0.07), clinical benefit rate (RD 0.10; 95 % confidence interval 0.02 to 0.17) and 6-months TTP/PFS (RD 0.07 95 % confidence interval 0.04 to 0.10). However, the Grade 3-4 toxicity set by WHO was higher for the GEM combination group for neutropenia, thrombocytopenia and vomiting/nausea. It was concluded that gemcitabine-based combination therapy may improve the overall survival and palliation in optimal patients with advanced pancreatic cancer as compared with GEM alone [193].

To assess the effects of chemotherapy and/or radiotherapy in the management of pancreatic adenocarcinoma in people with inoperable advanced disease it was searched the Cochrane Central Register of Controlled Trials (CENTRAL), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) Group Trials Register (The Cochrane Library 2005, Issue 1); CANCERLIT (1975-2002); MEDLINE (1966 to 2005); and EMBASE (1980 to 2005). It was handsearched reference lists from trials revealed by electronic searches to identify further relevant trials. Randomised controlled trials (single- or double-blind) in patients with advanced inoperable pancreatic cancer, in which one of the intervention types (chemotherapy or radiotherapy) was contrasted with either placebo or another type of intervention. Studies comparing non-chemotherapy agents such as biological agents, hormones, immunostimulants, vaccines and cytokines were excluded. Studies were assessed for eligibility and quality. Data were extracted by groups of two independent reviewers, with conflicts resolved by a third reviewer. Study authors were contacted for more information. Fifty trials (7043 participants) were included. Chemotherapy significantly reduced the one-year mortality (odds ratio 0.37; 95 % confidence interval 0.25 to 0.57) when compared to bestsupportive care. Also, chemoradiation improved one year survival (0 % versus 58 %) when compared to best supportive care. There was no significant difference in one-year mortality for 5FU alone versus 5FU combinations (odds ratio 0.90; 95 % confidence interval 0.62 to 1.30); single-agent chemotherapy versus gemcitabine (odds ratio 1.34; 95 % confidence interval 0.88 to 2.02); or gemcitabine alone versus gemcitabine combinations (odds ratio 0.88; 95 % confidence interval 0.74 to 1.05). However, subgroup analysis showed that platinum-gemcitabine combinations reduced six-month mortality compared to gemcitabine alone (odds ratio 0.59; 95 % confidence interval 0.43 to 0.81). A qualitative overview suggested that chemoradiation produced better survivals than either best supportive care or radiotherapy. Chemoradiation treatment was associated with more toxicity. The authors concluded that chemotherapy appears to prolong survival in people with advanced pancreatic cancer and can confer clinical benefits and improve quality of life. Combination chemotherapy did not improve overall survival compared to single-agent chemotherapy. Gemcitabine is an acceptable control arm for future trials investigating scheduling and combinations with novel agents. There is insufficient evidence to recommend chemoradiation in patients with locally advanced inoperable pancreatic cancer as a superior alternative to chemotherapy alone [194].

Clinical trials on the effects of systemic chemotherapy for patients with advanced pancreatic cancer have not been shown to have consistent benefits. A systematic review and meta-analysis was therefore conducted to examine this issue. All randomized trials on chemotherapy treatment for advanced pancreatic cancer published since the 1970's were identified by means of Medline and other major oncology databases. Systematic review of all trials was carefully conducted and data from trials with similar designs and regimens were pooled and grouped together in the benefit outcome analyses. Data for 5,365 patients from 43 randomized controlled trials were identified. Survival benefit over best supportive care was demonstrated in 5-FU-based chemotherapy in 9 randomized trials. However, trials that comparing 5-FU or other cytotoxic agent alone versus 5-FU-based combinations did not show any statistical differences, nor were various 5-FU-combinations comparing among themselves. On the other hand, gemcitabine was shown to improve survival and clinical benefit responses better than 5-FU and other new agents [195].

Summary: There are not less than seven honestly performed meta-analyses of combinations with gemcitabine. Taken together they show that gemcitabine still is the "gold standard" for palliative treatment of advanced pancreatic cancer, and that combinations with gemcitabine might be of some benefit. However, the differences of combinations compared to gemcitabine alone have been limited and with increased toxicity and costs.

5-Fluorouracil + combinations for advanced disease

5FU and oxaliplatin

A randomized phase II, open-label multicenter study evaluated oxaliplatin alone (OXA), infusional 5-fluorouracil alone (5-FU) and an oxaliplatin/infusional 5-FU combination (OXFU) in untreated, advanced pancreatic carcinoma with measurable disease. Patients received OXA [130 mg/m^2, 2-h intravenous (i.v.) infusion] alone, OXA combined with 5-FU (1000 mg/m^2/day, continuous i.v., days 1-4), or 5-FU alone, every 3 weeks. Sixty-three patients (42 males/21 females) were treated: 17 patients/52 cycles OXA, 31 patients/ 175 cycles OXFU, 15 patients/41 cycles 5-FU, with a median of three, six and two cycles/patient, respectively. Patient characteristics were similar in all arms. Median age was 57 years (range 21-75), and 83 percent of patients had Performance Status 0-1. Most patients (62 %) had moderate to well-differentiated tumors, 90 percent had metastatic disease, 81 percent with liver metastases. All responses (three partial responses; WHO) occurred in the OXFU arm (10 % response rate). Five of 32 patients evaluable for clinical benefit were responders (OXA, 14 %; OXFU, 21 %). Median time to progression and overall survival were higher in the combination arm (4 and 9 months, respectively) than either single-agent arm (OXA, 2 and 3 months; 5-FU, 2 and 2 months, respectively). Moderate hematotoxicity without morbidity was seen in all arms. Two OXFU patients had grade 3 oxaliplatin neurosensory toxicity. The authors concluded that with a 10 percent response rate, median overall survival of 9 months and an encouraging safety profile, the OXFU combination is effective, appears superior to infusional 5-FU and warrants further studies in patients with advanced pancreatic cancer [196].

Comment: The combination of 5FU and oxaliplatin might be better than 5FU alone.

5FU and cisplatin

In a previous phase II trial, 5-fluorouracil (5-FU) plus cisplatin (FUP) yielded a 27 percent response rate and a 29 percent survival rate at 1 year. One study therefore aimed to compare FUP with 5-FU alone, which was the control arm in former Mayo Clinic trials. Patients with untreated cytologically or histologically proven metastatic or locally advanced adenocarcinoma of the pancreas were deemed measurable or evaluable. Chemotherapy regimens consisted of a control FU arm (5-FU 500 mg/m^2/day for 5 days) and the investigational FUP arm (continuous 5-FU 1000 mg/m^2/day for 5 days plus cisplatin 100 mg/m^2 on day 1 or day 2). In both arms, chemotherapy was repeated at day 29. Two-hundred and seven patients from 18 centres were randomised: 103 in the FU arm and 104 in FUP arm. Treatment arms were balanced with respect to performance status grade 0-1 (83 % vs 86 %, respectively) and the presence of metastases (92 % vs 89 %, respectively). The median number of cycles administered was two in both arms (range 0-14). Five patients did not receive any chemotherapy and 45 received only one cycle. Toxicity (WHO grade 3-4) was significantly lower with FU than with FUP (20 % vs 48%), as was neutropenia (6 % vs 23 %), vomiting (4 % vs 17 %) and toxicity-related deaths (one versus four early in the trial). The response rate was low in both arms, but superior in the FUP arm: 12 percent versus 0 percent, which was a significant difference. The survival rates at 6 months were 28 percent and 38 percent for the FU and FUP arms, respectively, and 1-year survival rates were 9 percent and 17 percent, which was not statistically different. On the other hand, one-year progression-free survival was 0 percentwith FU versus 10 percent with FUP, which was statistically different. The authors concluded that in advanced pancreatic carcinomas with a poor prognosis, FUP was superior to FU in terms of response and progression-free survival, but not in terms of overall survival [197].

The objective of one phase III study was to compare the safety and efficacy of FLP, modulation of 5-fluorouracil by folinic acid or leucovorin (LV) and cisplatin, versus FP, 5-FU combined with cisplatin, as a first line chemotherapy in advanced oesophageal, gastric and pancreatic cancer. 232 patients with measurable lesions were randomised to receive at the first cycle either FP (arm A: 5-FU 800 mg/m^2/d in continuous infusion 5 days and cisplatin 100 mg/m^2 on day 1 or 2), or FLP (arm B: leucovorin, 100 mg/m^2/d in bolus 5 days, followed by 5-FU 350 mg/m^2/d in 1 h infusion 5 days and cisplatin 100 mg/m^2 on day 1 or 2). In case of no grade 3-4 haematological and diarrhoea toxicity, the dose of 5-FU was increased to 1000 mg/m^2/d and 400 mg/m^2/d in the two arms respectively, for the subsequent cycles until disease progression. There were 97 pancreatic adenocarcinoma, 19 squamous cell carcinoma of the oesophagus, 19 oesophageal adenocarcinoma, and 91 gastric adenocarcinoma. Safety remained acceptable and comparable in the two arms except for the severe grade 3-4 mucositis, which was lower in arm B (5 versus 16 %, p<0.009). Efficacy in terms of tumour response and survival was similar in the two arms, showing an objective response rate (after external review) of 19 percent (95 % confidence interval 11-26 %) in arm A versus 15 percent (95 % CI 9-22 %) in arm B, an overall median survival of 24 weeks in arm A versus 25 in arm B (p = 0.83) and a progression-free median survival of 12.4 weeks vs. 12.1 in arms A and B. This means that the FLP regimen is substantially equivalent to FP in terms of safety and quality of life, as well as for antitumour efficacy in these carcinomas [198].

Phase II trials of combined 5 fluorouracil, leucovorin and cisplatin have demonstrated an 18-28 percent response rate in advanced pancreatic carcinomas. It was now investigated the effect of this chemotherapy regime on patients' survival. The patients included had an advanced and proven pancreatic adenocarcinoma. The trial was multicentric, prospective and randomized. It compared a 5-day course of leucovorin (200 mg/m^2/day), 5-fluorouracil (375 mg/m^2/day) and cisplatin (15 mg/m^2/day) repeated every 21 days (23 patients) with a control group (22 patients). The main end points were survival time. The combination of leucovorin, 5-fluorouracil and cisplatin failed to demonstrate any advantage of this regimen compared with supported care alone. Median survival times were 9 months (SD $\pm$ 2) and 7 months (SD $\pm$ 1), respectively. The modulation of 5-fluorouracil by leucovorin and cisplatin was well tolerated with moderate toxic effects. It was concluded that this multicentric trial failed to demonstrate any advantage of the evaluated chemotherapy regime in the palliative treatment of cancer of the exocrine pancreas [199].

Summary: The combination of 5FU and cisplatin does not increase survival time compared to 5FU alone.

5FU, cisplatin and interferon

A randomised phase II study of 5-fluorouracil (5-FU) plus cisplatin (CDDP) with or without alpha-interferon 2b was performed in patients with pancreatic cancer with measurable metastatic disease outside the pancreas. The treatment in arm A consisted of cisplatin (100 mg/m^2) on day 1, followed by a continuous infusion of 5-FU 1000 mg/m^2 for 4 days and in arm B the same treatment was given plus alpha-interferon 2b in a dose of 3 million units/day subcutaneously from day 1 for 5 days. Thirty-six patients were entered in the trial, 18 in each arm. In arm B only 15 patients were eligible. No responses were observed in the 5-FU/CDDP arm and only 2 partial responses were achieved in the interferon-arm, lasting 27 and 32 weeks, respectively. Both treatment arms showed considerable toxicity. It had to be concluded that both treatment regimens have little activity and cannot be recommended [200].

Summary: The combination of 5FU, cisplatin and interferone does not increase survival time compared to 5FU alone.

5FU, folinic acid and ifosfamid

The Italian Oncology Group for Clinical Research (GOIRC) randomized 55 naive patients with advanced pancreatic cancer between intravenous 5-fluorouracil 400 mg/m^2, days 1-5 and folinic acid (FA) 200 mg/m^2, days 1-5 alone, using Machover's schedule, or with 5FU, FA, and ifosfamide (IFO) 5 g/m^2, day 1 and Mesna. In both arms, treatment was repeated every 28 days. Fifty-one patients were evaluable for response. The overall response rate was 6 percent (3 out of 51), 1 out of 29 (3 %) complete response in the arm with 5FU plus FA, and 2 out of 22 (9 %) partial responses in the arm with IFO. The duration of response rate was 39, 55, and 74 weeks, respectively. Median survival time was 21 weeks (range, 4-83 weeks) for 5FU/FA and 16 weeks (range, 3-106 weeks) for the FU/FA/IFO arm. Diarrhea, mucositis, and vomiting occurred in the majority of patients. One patient died due to toxicity. The combination of 5FU plus FA failed to demonstrate therapeutic activity in patients with and was associated with moderate to severe toxicity that could lower the quality of life of these patients. Ifosfamide did not potentiate the activity of this combination. Neither of these combinations should therefore be considered for treatment of patients with advanced pancreatic cancer [201].

> *Summary: The combination of 5FU and ifosfamid does not increase survival time compared to 5FU alone.*

5FU and mitomycin C

To compare (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin (MMC) in patients with advanced pancreatic cancer in a multicenter, prospectively randomized study 208 were randomized to PVI 5-FU (300 mg/m^2/d for a maximum of 24 weeks) or PVI 5-FU plus MMC (7 mg/m^2 every 6 weeks for four courses). The major end points were tumor response, survival, toxicity, and quality of life. The two treatment groups were balanced for baseline demographic factors, and 62 percent had metastatic disease. The overall response rate was 8 percent (95 % confidence interval 3 % to 14 %) for patients treated with PVI 5-FU alone compared with 18 percent (95 % confidence interval 10 % to 25 %) for PVI 5-FU plus MMC, which was a statistically significant difference. Median failure-free survival was 3 months for PVI 5-FU and 4 months for PVI 5-FU plus MMC, i.e. not significant different. Median survival was 5 months for PVI 5-FU and 7 months for PVI 5-FU plus MMC, which was not different. Toxicities in both arms were mild. There was a significant increased incidence of neutropenia in the 5-FU plus MMC arm, although no differences in infection were seen. No patients developed hemolytic uremic syndrome. Global quality of life improved significantly after 24 weeks of treatment compared with baseline for patients receiving 5-FU plus MMC, although there was no statistically significant difference between arms. The authors concluded that protracted venous infusion of 5-FU plus mitomycin C resulted in a superior response rate in comparison with 5-FU alone in advanced pancreatic cancer, but this did not translate into a survival advantage [202].

A randomized trial was conducted by the Southwest Oncology Group (SWOG) in advanced carcinoma of the stomach and pancreas and published in 1979. Patients were assigned to receive monthly 5-fluorouracil 96-hour continuous infusions with either bolus mitomycin C or oral methyl-CCNU. Mitomycin C and methyl-CCNU were administered every eight weeks. The 5 FU-mitomycin combination produced a 22 percent response rate in disseminated pancreatic carcinoma. The combination of infusion 5 FU and methyl-CCNU achieved responses in 5 percent of pancreatic tumors. There was no significant difference in survival between limbs. In pancreatic carcinoma median survival on the mitomycin limb was 19 weeks as compared to 17 weeks on the methyl-CCNU program. Leukopenia was greater for the first course on the mitomycin limb. Regression analysis demonstrated that performance status was the most important pretreatment characteristic for predicting survival in both

tumors. Neither 5 FU infusion combination appears to significantly alter the dismal prognosis of advanced upper gastrointestinal neoplasms [203].

Summary: The combination of 5FU and mitomycin C does not increase survival time compared to 5FU alone.

5FU, doxorubicin and mitomycin C (FAM)

The efficacy of 1/2 FAM, which consists of 5-fluorouracil (5-FU), adriamycin (ADM) and mitomycin C (MMC), was compared with that of palliative treatment in patients with unresectable pancreatic and biliary tract carcinomas in a multicenter randomized trial. The patients assigned to 1/2 FAM group were treated with 5-FU 200 mg/m^2/day, ADM 15 mg/m^2/day and MMC 5 mg/m^2/day, all intravenously. These three drugs were given concurrently as the initial dose within a week after palliative operation, and this regimen was repeated for at least 2 whole courses, at 4-week intervals before the next course of therapy. Those randomized to the control group were subjected to palliative treatment alone. Completely eligible for analysis were 42 cases of the 1/2 FAM group and 41 of the control group. There was no significant difference between the groups with respect to the overall and differentiated survival times according to the tumor sites and the clinical efficacy. As for the duration of 50 percent inhibition of tumor progression, a significantly better outcome was obtained in 1/2 FAM group. Tumor progression was most significantly inhibited in patients with gallbladder carcinoma. In 1/2 FAM group, tumor reduction was achieved in 1 complete and 2 partial responses. The most frequent adverse reaction was gastrointestinal manifestations, along with diarrhea and alopecia. 1/2 FAM did not contribute to the life prolongation, but inhibited the tumor progression for a significantly longer duration and, to a lesser extent, reduced the tumor size in unresectable pancreatic and biliary tract carcinomas [204].

Forty-three patients with irresectable advanced pancreatic cancer were randomized to receive chemotherapy using a combination of 5-fluorouracil, adriamycin and mitomycin C or no chemotherapy. Groups were well matched with regard to age, extent of disease and performance status on entry. Chemotherapy was well tolerated and, although common, side-effects were usually mild. Psychological measurements based on the Hospital Anxiety and Depression score were made in 31 patients. These showed significantly less depression but not anxiety in the treated group immediately after randomization and following 2 months of chemotherapy. Median survival in the treated group was 33 (range 9-80) weeks compared with 15 (range 1-62) weeks in the untreated group, which was a significant difference [205].

The modified FAM (5-fluorouracil (5-FU) + adriamycin (ADR) + mitomycin C (MMC)) therapy (FAM group) was compared with 5-FU mono-therapy (F group) by multi-institutional randomized trial in the patients with cancer of the pancreas or the biliary tract who underwent non-resection. The patients in FAM group received 6 mg/m^2 intravenously, MMC during operation, 310 mg/m^2 intravenously, 5-FU for 5 days in the 1st and 3rd postoperative weeks and 12 mg/m^2 intravenously, and ADR in the 2nd postoperative week. Those in F group received only 5-FU course in the administration schedule of FAM group. Among the cases which completed respective whole administration schedules there were 35 cases in FAM group and 36 in F group. There were no partial response observed in neither groups, and there was no significant difference between groups with respect to overall survival duration, and clinical effect. Primary adverse effects were alimentary symptoms and hepatic dysfunction, neither of which was serious, and there was no difference between groups except that hair loss was observed significantly more often in the FAM group [206].

The efficacy of combination chemotherapy, which consists of fluorouracil, doxorubicin and mitomycin, was compared with that of palliative surgery-only in patients (control) having non-resectable pancreatic and biliary carcinomas in a multicenter randomized trial. The patients were assigned to combination chemotherapy consisting of concomitant 5-fluorouracil 200 mg/m^2, doxorubicin 15 mg/m^2, and mitomycin 5 mg/m^2 by intravenous administration. This combination chemotherapy was given concurrently as the initial dose within 1 week after palliative operation, and this regimen was repeated for at least 2 whole courses at 4-week intervals before the next course of therapy. Forty-two cases of this combination chemotherapy group and 41 of the control group were completely eligible for analysis. Regarding the overall 50 percent inhibition of tumor progression and that of gallbladder carcinoma, there were significantly better outcomes in the modified FAM therapy group. In this group, tumor reduction was achieved in 1 complete response and 2 partial response patients. With respect to the overall and differentiated survival times according to the tumor sites and the clinical efficacy, there was no difference between the groups. The most frequent adverse reactions were gastrointestinal manifestations such as anorexia, nausea, vomiting, and diarrhea; also noted was alopecia [207].

In this multicenter randomized trial, the efficacy of combination chemotherapy using 5-fluorouracil, doxorubicin and mitomycin C (arm A) was compared with that of 5-fluorouracil alone (arm B) in 81 patients with nonresectable carcinomas of the pancreas or biliary tract. There were no significant differences between treatment arms regarding the median time to progressive disease, median survival time, palliative effects or toxicities. It was concluded that combination chemotherapy is feasible but cannot be recommended [208].

One hundred ninety-six patients with advanced pancreatic cancer were randomized to receive one of two combination chemotherapy programs: FAM (5-fluorouracil, doxorubicin, and mitomycin C) or FSM (5-fluorouracil, streptozotocin, and mitomycin C). Patient characteristics were comparable in both groups. Overall response rates for those with measurable disease (14 % on FAM, 4 % on FSM) were not significantly different. There was no significant difference in overall survival between patients treated with FAM and FSM (median survivals of 26 and 18 weeks, respectively). Survival benefits of FAM were significant only for patients with measurable disease. Toxicity of both regimens was acceptable and comparable, aside from greater renal toxicity and more nausea and vomiting with FSM [209].

Three hundred five patients with advanced pancreatic and gastric carcinoma were randomly assigned to treatment with fluorouracil, fluorouracil plus doxorubicin (FA), or fluorouracil plus doxorubicin plus mitomycin C (FAM). All regimens were equivalent with regard to patient survival. There was no reasonable likelihood that either the FA or FAM regimen could produce a meaningful survival advantage over fluorouracil alone. Interval to disease progression, objective response rates, and palliative effects (improved performance, body weight, or symptoms) were essentially equivalent among the three regimens. With regard to toxicity, the FAM regimen produced more anorexia, nausea, vomiting, leukopenia, thrombocytopenia, and cumulative bone marrow suppression. Fluorouracil alone produced more stomatitis and diarrhea. Because of a failure to produce improved survival or palliation, unrewarded toxicity, and excessive cost, neither the FA nor FAM regimen can be recommended for the treatment of advanced pancreatic or gastric cancer, according to the authors [210].

Summary: There are today several large and well performed studies on FAM, and the over-whelming data speak in favor of no benefit for this rather toxic combination in patients with advanced pancreatic cancer.

5FU, leucovorin and etopside

The aim of one study was to estimate any gain in the quantity and quality of life produced by chemotherapy in patients with pancreatic and biliary cancer. Between 1991 and 1995, 90 eligible patients with pancreatic or biliary cancer were randomized to either chemotherapy in addition to best supportive care or to best supportive care. Chemotherapy was allowed in the latter group if the supportive measures did not lead to palliation. Chemotherapy was either sequential 5-fluorouracil/leucovorin combined with etoposide (FELv) or, in elderly and poor performance patients, the same regimen without etoposide (FLv). Quality of life was evaluated with the EORTC-QLQ-C30 instrument. Mean scale scores in the QLQ-C30 improved more often/deteriorated less frequently in the chemotherapy group than in the best supportive care group. More patients in the chemotherapy group (36 %, 17/49) had an improved or prolonged high quality of life for a minimum period of 4 months compared to those in the best supportive care group (10 %, 4/41), which was a significant difference Overall survival was significantly longer in the chemotherapy group (median 6 vs 3 months). Also, the quality-adjusted survival time was significantly longer for patients randomized to chemotherapy (median 4 vs 1 month). The effects were seen both in pancreatic and biliary cancer [211].

Comment: The combination of 5FU and etopside showed a positive effect, but as the study ended in 1995 and have had no followers one must be a little skeptical.

5FU and streptozotocin

By random assignment a total of 176 eligible patients with advanced nonmeasurable pancreatic carcinoma were treated with 5-fluorouracil (5-FU) either alone or in combination with a nitrosourea (streptozotocin), in combination with a "lactone" (spironolactone), or in combination with both. The median survival period for all pancreatic carcinoma patients was 17 weeks. The addition of the nitrosoureas or the lactones or a combination of both produced no improvement in length of patient survival for either primary carcinoma when compared to treatment with 5-FU alone [212].

One hundred and sixteen patients with advanced and metastatic adenocarcinoma of the pancreas were randomized to treatment with combined streptozotocin and 5-fluorouracil or combined streptozotocin and cyclophosphamide. Toxic reactions to each regimen were qualitatively similar and consisted of nausea and vomiting during the time of treatment and subsequent leukopenia and thrombocytopenia. Renal toxicity was less frequent and only rarely severe. Among 51 eligible and evaluable patients treated with the streptozotocin-cyclophosphamide combination, 12 percent showed objective response and among 42 patients treated with streptozotocin + 5-fluorouracil, 12 percent showed objective response. The streptozotocin + 5-fluorouracil-treated patients showed a slight advantage in survival, but the authors concluded that neither regimen can be considered of substantive value to the patient with advanced pancreatic carcinoma [213].

Summary: Streptozotocin did not increase survival in combination with 5FU enough to balance the increased costs and toxicity.

5FU, streptozotocin and mitomycin C

A phase III comparison of cisplatin, cytosine arabinoside, and caffeine (CAC) versus standard treatment using streptozotocin, mitomycin, and 5-fluorouracil (SMF) was performed. Eighty-two patients with advanced pancreatic cancer were entered into this random assignment trial. The two treatment arms were well balanced for the usual prognostic factors. Although the acute (e.g. nausea and vomiting) toxicities of CAC were greater than those of SMF, both groups of patients tolerated treatment resonably well. Ninety percent of patients were evaluable for response. Two patients (6 %) on the CAC treatment arm (95 %

confidence interval, 0 % to 15 %) and four patients (10 %) on the SMF treatment arm (95 % CI 1 % to 22 %) had objective responses (partial response in measurable disease or improvement in evaluable disease). No complete remissions were observed. The 95 percent confidence limits of response for CAC and SMF overlapped. The median duration of survival for all patients on the SMF treatment arm was 10 months, and 5 months for the CAC treatment arm, which was a significant difference [214].

A prospective randomized trial comparing streptozotocin, mitomycin C, and 5-FU (SMF) with mitomycin C and 5-FU (MF) in patients with advanced pancreatic cancer was performed. In patients with measurable disease the response rates were 34 percent (19/56) to SMF, and 8 percent (5/60) to MF, which was a significant difference. Median survivals were similar, however, 18 versus 17 weeks. Median survival of patients responding to chemotherapy was 33 weeks, and for nonresponders it was 17 weeks, which was significantly different. In patients with nonmeasurable disease, median survivals were 21 weeks (SMF) and 18 weeks (MF). Patients surviving greater than or equal to 48 weeks, however, appeared to be increased in the SMF arm (14 patients) compared to the MF (7 patients). Toxicity was moderate for both regimens, with SMF having greater gastrointestinal and renal toxicity [215].

> *Summary: In some rather limited studies the combinations of 5FU, streptozotocin and mitomycin C there were some promising results, but there has been little follow-up on these issues, which is suspicious.*

"The Mallison regimen"

Forty patients with inoperable pancreatic cancer were included in a prospective, randomised, controlled trial of multiple chemotherapy. The survival of 19 untreated control patients was compared with that of 21 patients who received an initiation course of intravenous fluorouracil, cyclophosphamide, methotrexate, and vincristine given over five days followed by intravenous fluorouracil and mitomycin given over three or five days at six-week intervals thereafter. Median survival in treated patients was 44 weeks, which was significantly longer than the nine weeks seen in controls. In patients without metastases median survival was 48 weeks in the treated group and 12 weeks in controls. In patients with metastases it was 30 weeks in treated patients and seven weeks in controls. The treatment was well tolerated and seemed to confer a significant prolongation of survival, comparing favourably with previous reports of chemotherapy with or without radiotherapy [216].

5FU versus "the Mallinson regimen"
One hundred eighty-seven patients with histologically proven advanced pancreatic adenocarcinoma were randomly assigned to therapy with 5-fluorouracil (5-FU) alone, to the Mallinson regimen (combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C), or to combined 5-FU, doxorubicin, and cisplatin (FAP). Patients with both measurable and nonmeasurable disease were included and the primary study end point was survival. Among 41 patients with measurable disease, objective response rates were 7 percent for 5-FU alone, 21 percent for the Mallinson regimen, and 15 percent for FAP. The median interval to progression for each of the three regimens was 3 months. Survival curves intertwined with the median survival times for 5-FU alone and the Mallinson regimen at 5 months and for FAP at 4 months. Compared with 5-FU alone, both the Mallinson regimen and FAP produced significantly more toxicity, and therefore the authors could not recommend either the Mallinson regimen nor FAP as therapy for advanced pancreatic carcinoma [217].

> *Comment: "The Mallinson regimen" got a lot of attention in 1980 and 1990, but has since then not been heard of.*

5FU and CCNU

Between the years 1973-1977, 152 male patients from 28 participating Veterans Hospitals with histologically proven nonresectable cancer of the pancreas were randomized in a two-arm study. The treated group was to receive combination chemotherapy with 5-FU and CCNU, and the controls were to receive no chemotherapy. Both groups were comparable with respect to age, amount of weight loss, extent of histologically proved metastases, and operation performed. In the treatment group, drug therapy was begun between 10 and 60 days postoperatively. Intravenous 5-FU, 9 mg/kg, was administered on five consecutive days, and CCNU, 70 mg/m^2, was given orally on the first day of each course. In the absence of toxicity, the course was repeated every six weeks for life; 146 drug courses were given. The incidence of toxicity was not great. One or more toxic reactions were reported for one-third of the drug courses administered, but for the most part, these were mild. The most frequent toxic reaction was vomiting in 17 percent of the courses, and hematologic toxicity – primarily leucopenia – in 15 percent of the drug courses. There was no evidence of a beneficial effect on survival from drug treatment in the group as a whole or in any subgroup analyzed. The median survival of the control group was 4 months, and of the drug-treated group, 3 months [218].

5FU and N-(phosphonacetyl)-L-aspartic acid (PALA)

Fifty-two patients with advanced gastrointestinal malignancies who had not received previous chemotherapy or radiation therapy were randomized to be treated either with 24-hour infusion of weekly fluorouracil or the same plus N-(phosphonacetyl)-L-aspartic acid (PALA). Forty-seven patients were evaluable for the assessment of toxicity and antitumor activity. PALA was administered as an intravenous bolus over 15 minutes at a fixed dose, 250 mg/m^2. The latter agent was administered 24 hours before the start of 5-FU infusion. 5-FU was initially administered at 750 mg/m^2 and was incrementally increased to 3,400 mg/m^2. In both arms of the randomized study, the courses were repeated every week. In both arms of the study, ataxia and myelosuppression were the dose-limiting toxic effects. At 5-FU dose of 3,400 mg/m^2, one patient in each arm developed grade 3 hematologic toxicity. Other reversible side effects included grade 2 skin changes, nausea, and vomiting. During the administration of 2,600 mg/m^2 of 5-FU over 24 hours, the steady state plasma 5-FU concentration was approximately 20 mumol/L. The maximum tolerated dose (MTD) for 5-FU for protracted treatment is 2,600 mg/m^2 in either arm of the study. Therapeutic response was predominantly seen in the combination arm: there were two patients with complete response and 11 patients with partial response of 28 patients in the study. In the 5-FU alone arm there were four PR and 19 patients in the study [219].

5FU and carmustine

A prospective randomized trial between two drug regimens in 38 patients with advanced pancreatic carcinoma was published in 1978. The two-drug regimen consisted of carmustine and fluorouracil. The survival rate and response to these two drugs was compared to a three-drug regimen consisting of these same two drugs plus spironolactone. Objective partial responses were rare in both groups, being 3/18 in the two-drug group and 2/20 in the three-drug group. Life table analysis in previously untreated patients from time of treatment shows longer survival for the three-drug group, but this difference was not statistically significant [220].

5FU and radiation

The purpose of one study was to evaluate whether external-beam radiotherapy (EBRT) with concurrent continuous 5-fluorouracil (5-FU) infusion affects the length and quality of survival in patients with locally unresectable pancreatic cancer. Thirty-one patients with histologically proven locally advanced and unresectable pancreatic cancer without distant metastases were evaluated in this prospective randomized trial. Sixteen patients received EBRT (50.4 Gy/28 fractions) with concurrent continuous infusion of 5-FU (200 mg/m^2/day), whereas 15 patients received no chemoradiation. The length and quality of survival was analyzed and compared for the two groups. The median survival of 13 months and the 1-year survival rate of 53 percent in the chemoradiation group were significantly better than the respective 6 months and 0 percent in the group without chemoradiotherapy. The average monthly Karnofsky score, a quality of life indicator, was 77 in the chemoradiation group, which was significantly higher than the 66 in the group without chemoradiotherapy. The number of hospital days per month of survival was significantly less in the chemoradiation than in the no-therapy group (12 vs 19 days). In the chemoradiation group, 5 patients (31 %) had a partial response, and 9 (56 %) had radiologically stable disease at a median duration of 6 months. The patients who had chemoradiation had a lower rate of liver and peritoneal metastases than patients without chemoradiotherapy (31 % vs 64 %). Of 10 patients who experienced pain before chemoradiation, 8 (80 %) received pain relief that lasted a median of 5 months. This means that external-beam radiotherapy with concurrent continuous 5-FU infusion increased the length and quality of survival as compared to no chemoradiotherapy and provided a definite palliative benefit for patients with unresectable pancreatic cancer [221].

One hundred ninety-one patients with pathologically confirmed, locally unresectable adenocarcinoma of the stomach (57 patients) and pancreas (91 patients), were randomly allocated to therapy with 5-fluorouracil alone, 600 mg/m^2 intravenously once weekly, or radiation therapy, 4,000 rad, plus adjuvant 5-FU, 600 mg/m^2 intravenously, the first three days of radiotherapy, then follow-up maintenance 5-FU, 600 mg/m^2, weekly. Forty-three patients (22 %) could not be analyzed because of ineligibility or cancellation, thus 148 patients were evaluable. The median survival time was similar for both treatment programs and for both types of primary carcinoma, and was as follows: pancreatic primary carcinoma, 5-FU, 8 months; 5-FU plus radiotherapy, 8 months. Substantially more toxicity was experienced by patients treated with the combined modality arm than by those patients receiving 5-FU alone. The toxicity experienced by patients with pancreatic primary carcinoma treated with 5-FU was 27 percent, and the combined modality arm was 51 percent [222].

From 1981 to 1987, 87 patients with histologically confirmed pancreatic adenocarcinoma, unresectable but confined to the pancreatic region, were randomized to two treatments. The standard treatment was 40-50 Gy external-beam radiation therapy (EBRT) to gross tumor plus potential microscopic tumor with a 5 Gy boost to gross tumor plus a 1.5-2.0 cm margin, using multiple fields and 5-fluorouracil 500 mg/m^2/d intravenously by rapid infusion. The 5-FU was given each of the initial 3 days of each of three 20 Gy radiation courses. The experimental treatment used identical radiation fields, but the two Gy daily radiation fractions were administered in a continuous course to a total dose of 50 Gy. Hycanthone was administered 60 mg/m^2 intravenously within 2 to 4 hr during each day of the 5-day course of infusions during the first and fifth weeks of radiation therapy. There was no statistically significant difference between treatment arms in survival or disease-free survival. Seven percent of hycanthone-treated patients demonstrated hepatic toxicity which was usually mild in nature. There was, however, one death due to hepatic toxicity [223].

In a study published in 1981, 194 eligible and evaluable patients with histologically confirmed locally unresectable adenocarcinoma of the pancreas were randomly assigned to therapy

with high-dose (6000 rads) radiation therapy alone, to moderate-dose (4000 rads) radiation + 5-fluorouracil (5-FU), and to high-dose radiation plus 5-FU. Median survival with radiation alone was only 6 months from date of diagnosis. Both 5-FU-containing treatment regimens produced a highly significant survival improvement when compared with radiation alone. Forty percent of patients treated with the combined regimens were still living at one year compared with 10 percent of patients treated with radiation only. Survival differences between 4000 rads plus 5-FU and 6000 rads plus 5-FU were not significant with an overall median survival of 10 months [224].

In 1979 was published a study on 106 patients with histologically confirmed pancreatic carcinoma that were randomized to one of three radiation treatment programs: 1) radiation therapy alone to 6000 rads; 2) 6000 rads plus 5-FU; or, 3) 4000 rads plus 5-FU. Patient survival was the primary study parameter. Both 4000 rads plus 5-FU and 6000 rads plus 5-FU were associated with a significantly longer patient survival than 6000 rads alone. Respective median survivals were 36 weeks, 40 weeks, and 20 weeks. The survival difference between 4000 rads plus 5-FU and 6000 rads plus 5-FU was not statistically significant at the time point selected [225].

> *Summary: Most studies on radiation plus 5FU are today rather old, and their results must be taken with some caution as radiation today is different. However, taken together it seems unlikely that radiation together with 5FU should have a significant positive effect on advanced pancreatic cancer.*

5FU, radiation and metyl-CCNU

A prospectively randomized trial in advanced gastric and pancreatic carcinoma compared multi-drug chemotherapy, with and without radiotherapy to the local lesion, in terms of median survival and toxicity. Of 29 patients with gastric adenocarcinoma, 14 were randomized to receive 5-FU and methyl-CCNU, and 15 to receive 5-FU and local radiotherapy to a dose of 4600 rad, and then methyl-CCNU. Thirty patients with advanced adenocarcinoma of the pancreas were similarly randomized. There was no significant difference between the two arms of the gastric or pancreatic adenocarcinoma groups, with a 8 months and 7 months median survival in the pancreatic carcinoma patients. Complications were minimal in both groups. There was more hematopoietic depression in the radiation-treated patients, but none had radiotherapy discontinued because of toxicity [226].

5FU versus octreotide

The purpose of one study was to compare the antitumor activity of the somatostatin analogue octreotide to 5-fluorouracil chemotherapy in a phase III setting. Eighty-four patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 and limited tumor volume were randomized to receive octreotide 200 microg three times daily or 5-fluorouracil with or without leucovorin. After the first 12 patients had been randomized to octreotide, the dose in the remaining patients was increased to 500 microg three times daily. This change was based on early reports in other studies, suggesting that the original dose may not have been effective and that higher doses of octreotide were well tolerated. A planned interim analysis performed after 84 patients were enrolled demonstrated inferior time to progression and survival for the patients randomized to octreotide. Further accrual to the octreotide arm of this protocol was therefore terminated. Octreotide in doses of 200-500 microg three times daily does not delay progression or extend survival in patients with advanced pancreatic cancer compared with treatment with 5-fluorouracil with or without leucovorin [227].

FOLFOX

It was conducted a randomised phase II study of the modified FOLFIRI.3 (mFOLFIRI.3; a regimen combining 5-fluorouracil (5-FU), folinic acid, and irinotecan) and modified FOLFOX (mFOLFOX; a regimen combining folinic acid, 5-FU, and oxaliplatin) regimens as second-line treatments in patients with gemcitabine-refractory pancreatic cancer. The primary end point was the 6-month overall survival rate. The mFOIFIRI.3 regimen consisted of irinotecan (70 mg/m^2; days 1 and 3), leucovorin (400 mg/m^2; day 1), and 5-FU (2000 mg/m^2; days 1 and 2) every 2 weeks. The mFOLFOX regimen was composed of oxaliplatin (85 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and 5-FU (2000 mg/m^2; days 1 and 2) every 2 weeks. Sixty-one patients were randomised to mFOLFIRI.3 (n=31) or mFOLFOX (n=30) regimen. The six-month survival rates were 27 percent (95 % confidence interval 13 to 46 %) and 30 percent (95 % confidence interval 15 to 49 percent), respectively. The median overall survival periods were 17 and 15 weeks, respectively. Disease control was achieved in 23 percent (95 % confidence interval 10 to 42 percent) and 17 percent patients (95 % confidence interval 6 to 35 %), respectively. The number of patients with at least one grade 3/4 toxicity was identical (11 patients, 38 %) in both groups: neutropenia (7 patients under mFOLFIRI.3 regimen vs 6 patients under mFOLFOX regimen), asthaenia (1 vs 4), vomiting (3 in both), diarrhoea (2 vs 0), and mucositis (1 vs 2). It was concluded that both mFOLFIRI.3 and mFOLFOX regimens were tolerated with manageable toxicity, offering modest activities as second-line treatments for patients with advanced pancreatic cancer, previously treated with gemcitabine [228].

> *Comment: FOLFOX have been given a lot of attention lately, but it seems that possible positive effects on advanced pancreatic cancer is limited*

Meta-analyses

In advanced pancreatic cancer, level one evidence has established a significant survival advantage with chemotherapy, compared to best supportive care. The treatment-associated toxicity needs to be evaluated. One study examined the secondary outcome measures for chemotherapy in advanced pancreatic cancer using meta-analyses. A systematic review was undertaken employing Cochrane methodology, with search of databases, conference proceedings and trial registers. The secondary end points were progression-free survival (PFS)/time to progression (TTP) (summarised using the hazard ratio), response rate and toxicity (summarised using relative risk). There was no significant advantage of 5FU combinations versus 5FU alone for TTP (hazard ratio 1.02; 95 % confidence interval 0.85 to 1.23) and toxicity. Progression-free survival (hazard ratio 0.78; 95 % confidence interval 0.70 to 0.88), TTP (hazard ratio 0.85; 95 % confidence interval 0.72 to 0.99) and overall response rate (relative risk 0.56; 95 % confidence interval 0.46 to 0.68) were significantly better for gemcitabine combination chemotherapy, but offset by the greater grade 3/4 toxicity thrombocytopenia (relative risk 1.94; 95 % confidence interval 1.32 to 2.84), leucopenia (relative risk 1.46; 95 % confidence interval 1.15 to 1.86), neutropenia (relative risk 1.48; 95 % confidence interval 1.07 to 2.05), nausea (relative risk 1.77; 95 % confidence interval 1.37 to 2.29), vomiting (relative risk 1.64; 95 % confidence interval 1.24 to 2.16) and diarrhoea (relative risk 2.73; 95 % confidence interval 1.87 to 3.98). There is no significant advantage on secondary end point analyses for administering 5FU in combination over 5FU alone. There is improved progression-free survival, time to progression and response rate, with gemcitabine-based combinations, although this comes with greater toxicity [229].

> *Summary: There is no significant advantage for administering 5FU in most combinations over 5FU alone.*

Epirubicin + combinations for advanced disease

In a randomized trial it was compared single-agent epirubicin with the FEM (5-fluorouracil, epirubicin, and mitomycin C) combination in patients with locally advanced and/or metastatic adenocarcinoma of the pancreas. Sixty patients previously untreated with radiotherapy or chemotherapy were randomly assigned to receive either 100 mg/m^2 epirubicin or FEM in the following doses: 5-fluorouracil, 600 mg/m^2 to a maximum of 1 g; epirubicin, 50 mg/m^2; mitomycin, 6 mg/m^2 to a maximum of 10 mg. Treatment was given every 28 days via intravenous bolus; because of its association with delayed myelotoxicity, mitomycin was given every other cycle. A total of 47 patients were evaluable for toxicity and survival, 22 who received FEM and 25 epirubicin. Preliminary results of this ongoing study show no difference in survival between the two arms. Toxicity has been easily managed. A similar number of patients in each arm had elevated serum bilirubin levels, but dose reductions of 50 percent allowed all these patients to continue treatment [230].

Sixty-nine unselected patients with locally advanced and metastatic carcinoma of the pancreas, who had not received previous chemotherapy or radiotherapy were randomised to receive either 5-fluorouracil, epirubicin and mitomycin C (FEM) or epirubicin. Survival was not significantly different in the two arms. Toxic reactions (WHO grade greater than 3) in the FEM and epirubicin arm respectively included nausea (2), (4), severe alopecia (1) (3) and leucopenia (1), (5), but none of these were statistically significant. The authors therefore suggested that combination chemotherapy should not be used in preference to single agent chemotherapy as standard treatment for locally advanced or metastatic cancer of the pancreas [231].

Summary: Epirubicin has so far had little impact on pancreatic cancer.

Irinotecane

There has been no established second-line treatment for advanced pancreatic cancer after gemcitabine failure. In view of the urgent need for such therapy, and since preclinical and phase I clinical data suggest an encouraging, potentially synergistic activity between raltitrexed and irinotecan, the present randomised phase II study was initiated. A total of 38 patients with metastatic pancreatic adenocarcinoma, who progressed while receiving or within 6 months after discontinuation of palliative first-line chemotherapy with gemcitabine, were enrolled in this study. They were randomised to 3-weekly courses of raltitrexed 3 mg/m^2 on day 1 (arm A) or irinotecan 200 mg/m^2 on day 1 plus raltitrexed 3 mg/m^2 on day 2 (arm B). The primary study end point was objective response, secondary end points included progression-free survival and overall survival, as well as clinical benefit response in symptomatic patients (n=28). In the combination arm, the confirmed objective response rate was 16 percent (three out of 19 patients had a partial remission; 95 % CI 3-40 %), which was clearly superior to that in the comparator/control arm with raltitrexed alone, in which no response was obtained. Therefore, the trial was already stopped at the first stage of accrual. Also, the secondary study end points, median progression-free survival (3 vs 4 months), overall survival (4 vs 7 months), and clinical benefit response (8 vs 29 %) were superior in the combination arm. The objective and subjective benefits of raltitrexed plus irinotecan were not negated by severe, clinically relevant treatment-related toxicities: gastrointestinal symptoms (42 vs 68 %), partial alopecia (0 vs 42 %), and cholinergic syndrome (0 vs 21 %) were more commonly noted in arm B; however, grade 3 adverse events occurred in only three patients in both treatment groups. The data indicate that combined raltitrexed plus irinotecan seems to be an effective salvage regimen in patients with gemcitabine-pretreated pancreatic cancer [232].

Comment: Gemcitabine and irinotecan might be of value in the treatment of advanced pancreatic cancer

Glufosfamid

A phase III trial evaluated the efficacy and safety of glufosfamide as compared with best supportive care (BSC) in this patient population. Patients were randomised to glufosfamide plus BSC or to BSC alone with baseline performance status as a stratification factor. The primary end-point was overall survival. Three hundred and three patients were randomised: 148 to glufosfamide plus BSC and 155 to BSC alone. There was an 18 percent increase in overall survival for glufosfamide that was not statistically significant: hazard ratio was 0.85 (95 % confidence interval 0.66 to 1.08). Median survival was 105 (range 5-875) days for glufosfamide and 84 (range 2 to 761) days for BSC. Grade 3/4 creatinine increase occurred in 6 patients on glufosfamide, including 4 with dosing errors. These results suggest low activity of glufosfamide in this very refractory patient population [233].

The activity of glufosfamide (beta-D-glucopyranosyl-N,N'-di-(2-chloroethyl)-phosphoric acid diamide) against pancreatic cancer was investigated in a multicentre, phase II clinical study. Chemotherapy-nai;ve patients with advanced or metastatic disease were treated with glufosfamide (5 g/m(2)) using a 1-h intravenous (i.v.) infusion every 3 weeks. Patients were randomised between active-hydration and normal fluids to evaluate the nephroprotective effect of forced diuresis. Patients experiencing >0.4 mg/dL (>35 micromol/l) increase in serum creatinine compared with their baseline value were taken off treatment for safety reasons. The evaluation of response was according to the Response evaluation criteria in solid tumours (RECIST). Blood sampling was performed for pharmacokinetic analyses. 35 patients from 13 institutions were registered over a 13-month period. A total of 114 treatment cycles (median 3, range 1-8) were administered to 34 patients; 18 patients were allocated to the hydration arm. Overall haematological toxicity was mild. Metabolic acidosis occurred in 2 patients treated in the active-hydration arm, grade 3 hypokalaemia was recorded in 5 patients and grade 3 hypophosphataemia in 4 patients. One patient had a grade 4 increase in serum creatinine level, concomitantly to disease progression. Active-hydration did not show a nephroprotective effect and the plasma pharmacokinetics of glufosfamide was not significantly influenced by hydration. Two confirmed partial remissions were reported (response rate 5.9 %; 95 % confidence interval 0.7-19.7 %) and 11 cases obtained disease stabilisation (32 %). An extra mural review panel confirmed all of the responses. Median overall survival was 5 months (95 % CI 4-7) and time to progression was 1.4 months (95 % CI 1.3-2.7). In conclusion, glufosfamide administered using a 1-h infusion every 3 weeks has a modest activity in advanced pancreatic adenocarcinoma. Haematological toxicity is particularly mild, but regular monitoring of renal function is recommended [234].

Summary: Glufosfamide as a treatment for pancreatic cancer might have a modest effect, but not more, and will not be recommended at this stage.

Sex-hormone influence

Flutamide

To assess whether flutamide, a pure androgen receptor blocking agent, improves survival in patients with pancreatic carcinoma and thus whether testosterone is a major growth factor for this tumour a prospective, randomised, double blind placebo controlled trial with 49 patients with a clinical diagnosis of pancreatic carcinoma was performed. Twenty-four patients received flutamide and 25 received placebo. Analysis of all patients at 6 months and 1 year

showed 14 and eight patients alive, respectively, in the flutamide group compared with 10 and one in the placebo group. After exclusion of those patients in both groups who received less than 6 weeks' treatment because of advanced disease and early death the comparable results were 14 (88 %) and eight (50 %) alive in the flutamide group compared with 10 (50 %) and one (5 %) in the placebo group. Median survival for all patients was 8 months in the flutamide group compared with 4 months in the placebo group. With the 6 week exclusions median survival was 12 months compared with 5 months, respectively. The author advocated that the study supported the concept that testosterone is a growth factor for pancreatic carcinoma and that blockade of androgen receptors offers an appropriate new approach to treatment [235].

In a small Indian study it was evaluated the impact of flutamide on survival of patients with unresectable pancreatic cancer. The single institution, randomized, double-blind, placebo controlled study compared flutamide in the dose of 250 mg three times daily (n=23) versus placebo (n=23) in patients with histologically proven, previously untreated unresectable pancreatic adenocarcinoma. The primary end point was overall survival; secondary endpoints included 6-month and 1-year survival rates, performance status and response rate. Both the groups were well matched with regards to demographic, disease related and treatment variables. This small sample sized study, failed to demonstrate a dramatic effect on survival with the use of flutamide. Median overall survival was 151 days with the use of flutamide as compared to 136 with placebo, which was a not significant difference. The 6-month survival rate was 39 percent in both arms of study and 1-year survival was 4 percent versus 13 percent for the flutamide group. There was no statistically significant difference in time to deterioration of performance status (flutamide 90 days versus placebo 68 days) and all patients died as a result of tumor progression [236].

Tamoxifen

Forty-four patients with biopsy-proven irresectable adenocarcinoma of the pancreas were recruited into a randomized placebo-controlled clinical trial of tamoxifen 20 mg twice daily. All patients were assessed at the time of diagnosis and at monthly intervals using the Karnofsky and the Hospital Anxiety and Depression scores for quality of life. Analysis of survival by life-tables and the log rank test revealed no significant difference in the duration of survival of patients treated with tamoxifen or placebo. Quality-of-life assessment revealed no significant difference between the groups. The authors concluded that tamoxifen does not confer significant benefit to patients with irresectable pancreatic cancer [237].

Between 1984 and 1987, 176 Norwegian patients with histologically verified unresectable pancreatic adenocarcinoma were randomized to double-blind treatment with oral tamoxifen (30 mg daily; 48 men and 44 women) or placebo (47 men and 37 women). Analysis of estrogen receptor activity in the carcinomas was not performed. There were no statistically significant differences between the two groups according to age, Karnofsky performance index, tumour node metastasis (TNM) stage, operative treatment or other patient characteristics. The tamoxifen or placebo treatment continued to death or to 10 months after accrual into the trial was stopped. In the tamoxifen group, the mean and median survivals were 205 and 115 days, respectively. These values did not differ statistically from the 192 and 122 days, respectively, observed in the placebo group. Additional retrospective analyses of gender and stage revealed no beneficial effect of tamoxifen upon survival. For women in stage III (any T N1 M0), mean and median survivals were 255 and 191 days, respectively, compared with values of 84 and 45 days, respectively, in the placebo group, which was a significant difference. After 2.5 years, three (7 percent) women in the tamoxifen group were still alive compared with no survivors in the placebo group. No male patients survived beyond 2.5 years. This therapeutic result in a small subgroup of women is probably incidental and not an effect of tamoxifen, according to the authors [238].

In a prospective controlled clinical trial, 108 patients with pancreatic adenocarcinoma were randomly allocated to receive tamoxifen 20 mg b.d., cyproteron acetate 100 mg t.d.s. or no active treatment. The median survival of those receiving tamoxifen was longer than either of the other two groups (5 compared to 4 and 3 months, respectively) but this difference did not achieve statistical significance. Cox regression analysis of 12 clinical and biochemical features showed that, for the entire group of patients, survival was significantly longer in younger patients, those undergoing surgical bypass and those with better initial performance status. However, even when adjustment was made to allow for the distribution of these prognostic variables within the three groups, the difference in survival still did not achieve statistical significance. No side-effects attributable to treatment were observed [239].

LHRH

Experimental studies have shown a significant inhibition of adenocarcinoma of the pancreas by gonadoliberin (luteinizing hormone-releasing hormone, LH-RH) and somatostatin. The aim of one prospective randomized study was to compare the potential value of somatostatin (250 micrograms every 8 hours), LH-RH (3.75 mg monthly), or combined, to a control group. One hundred sixty-three patients with adenocarcinoma of the pancreas who did not undergo resection for cure were divided into 4 groups that did not differ in terms of clinical, biologic, or pathologic data. The mean survival times were 6 months in the LH-RH plus somatostatin group, 6 months in the LH-RH group, 4 months in the control group, and 4 months in the somatostatin group. However, the life-table analyses for all randomized patients, and separately according to gender, the lymph node extension, and metastatic spread were not different between groups. Improvement of patient status was observed in 20 percent of the patients receiving hormone therapy without any difference noted between the treatment regimens. These disappointing results may be explained by the degree of extension of pancreatic carcinoma in the patients studied [240].

> *Summary: Treatment of pancreatic cancer with sex-hormone based drugs have so far not been successful.*

Drugs aiming at immunological effects

Interferon-alpha

Data from a phase II trial combining chemoradiotherapy with IFN-alpha (CapRI scheme) for adjuvant treatment of pancreatic carcinoma are encouraging. Therefore, a phase III trial comparing chemotherapy with the chemoradiotherapy with IFN-alpha scheme has been initiated in 2004. Translational research with a focus on immunomodulation is performed in parallel to the study. Blood and serum samples are taken at various time points. Patients in arm A (chemoradioimmunotherapy) receive a single low-dose-interferon injection before therapy to investigate the direct effect of IFN-alpha. So far samples from 44 patients have been investigated for surface molecule expression, cytokine levels, natural killer cell cytotoxicity, and antigen-specific Granzyme B release. Patients in arm A showed 1 day after IFN-alpha injection a significant increase in spontaneous cytotoxicity; this effect was fading after repeated injections. Furthermore, cells releasing Granzyme B after stimulation with CA 19.9 and MUC-1 protein increased under therapy. Five days after the first IFN-alpha injection, IL-12 and TNF-alpha serum levels peak. It was observed significant increases of monocytes, peripheral dendritic cells, CD40 cells, central and effector memory T cells, and CD8 cells, CD4 cells decreased during therapy. All these effects were only observed in arm A patients and none of them in arm B patients. In conclusion, it was observed an immediate activation of antigen-presenting cells and natural killer cells followed later on by antigen-specific activation [241].

Comment: The study shows that there is an immediate immunological reaction to the injection of interferon-alpha. However, if this correlate with the clinical course of the patients is not yet know, neither is it known if this is of benefit or a disadvanatge in combination with chemotherapy.

Interlukin-2

A cell-mediated immunodeficiency is demonstrated to occur in advanced cancer patients. Lymphocytopenia predicts a poor prognosis, moreover, the surgical trauma can worsen the impaired immune surveillance and favor disease recurrence. One study investigates the effectiveness of preoperative interleukin-2 administration to improve lymphocyte counts' postoperative recovery in pancreatic cancer. Thirty-one patients with pancreatic cancer who underwent radical surgery were randomized according to 3 different groups. Group A: 9 patients treated with human recombinant IL-2 subcutaneously at 9 million IU/day for 3 days before surgery; group B: 9 patients treated with IL-2 at 12 million IU/day for 3 days before surgery; group C: 13 patients treated with surgery alone. Assessment of total and T helper lymphocyte counts were studied at hospital admission and in 7th and 14th postoperative day. Toxicity of IL-2 treatment was mild in all groups. Postoperative lymphocytopenia was observed in group A and C, without statistical differences, whereas group B had mean lymphocyte levels within the normal values in the postoperative period. It was concluded that this preliminary result suggests that preoperative subcutaneously IL-2 immunotherapy at 12 million IU for 3 consecutive days before surgery is able to abrogate the effects of the surgical trauma and recover a normal immunofunction in pancreatic cancer patients [242].

In pancreatic cancer there is a severe suppression of the anticancer immunity that is further amplified by surgery-induced immunosuppression, evidenced by a decline in lymphocyte numbers during the postoperative period. Previous studies in colorectal cancer demonstrated that surgery-induced lymphocytopenia may be abrogated by a brief preoperative administration of IL-2. A new study included 30 consecutive patients who were randomized to be treated by radical surgery alone as a control group or by a preoperative immunotherapy with IL-2 (12 MIU/day subcutaneously for 3 consecutive days) plus surgery. Mean lymphocyte numbers significantly decreased in patients treated with surgery only, whereas it significantly rose in the IL-2-treated group. After a follow-up of 36 months, both the free-from-progression period and the overall survival were significantly higher in patients treated with IL-2. These preliminary results suggest that a short-period preoperative immunotherapy with IL-2 is sufficient to modify host tumor interactions in operable pancreatic cancer, with a subsequent abrogation of postoperative lymphocytopenia and a prolongation of overall survival [243].

Comment: Like interferon-alpha, interleukin-2 induces an immediate immunological reaction. However, if this correlate with the clinical course of the patients is not yet know, neither is it known if this is of benefit or a disadvanatge in combination with chemotherapy.

Taurolidine

The effect of additional treatment strategies with antineoplastic agents on intraperitoneal tumor stimulating interleukin levels is unclear. Taurolidine and Povidone-iodine have been mainly used for abdominal lavage in Germany and Europe. In the settings of three University Hospitals prospective randomized controlled trial 120 patients were randomly allocated to receive either 0.5 percent taurolidine/2,500 IU heparin (TRD) or 0.25 percent povidone-iodine (control) intraperitoneally for resectable colorectal, gastric or pancreatic cancers. Due to the fact that IL-1beta (produced by macrophages) is preoperatively indifferent in various gastrointestinal cancer types our major outcome criterion was the perioperative (overall) level

of IL-1beta in peritoneal fluid. Cytokine values were significantly lower after taurolidin lavage for IL-1beta, IL-6, and IL-10. Perioperative complications did not differ. The median follow-up was 50 months. The overall mortality rate (28 vs 25 %), the cancer-related death rate (17 vs 19 %), the local recurrence rate (7 vs 12 %), the distant metastasis rate (13 vs 18 %) as well as the time to relapse were not statistically significant different [244].

Garlic extract

Aged garlic extract has manifold biological activities including immunomodulative and antioxidative effects. It is used as a major component of nonprescription tonics and cold-prevention medicines or dietary supplements. The study's subjects were patients with inoperable colorectal, liver, or pancreatic cancer. In a randomized double-blind trial, aged garlic extract was administered to one group and a placebo was administered to another for 6 mo. The primary endpoint was a quality of life questionnaire based on the Functional Assessment of Cancer Therapy (FACT). The subendpoints were changes in the natural-killer (NK) cell activity the salivary cortisol level from before and after administering aged garlic extract. Out of 55 patients invited to participate in the trial, 50 (91 %) consented to enroll. They consisted of 42 patients with liver cancer (84 %), 7 patients with pancreatic cancer (14 %), and 1 patient with colon cancer. Drug compliance was relatively good in both the aged garlic extract and placebo groups. Although no difference was observed in quality of life, both the number of NK cells and the NK cell activity increased significantly in the aged garlic extract group. No adverse effect was observed in either group. The study showed that administering aged garlic extract to patients with advanced cancer of the digestive system improved NK cell activity, but caused no improvement in quality of life [245].

Interleukine and interferone

One paper presented the results of a prospective randomized study of targeting locoregional chemotherapy and targeting locoregional immunostimulation therapy implemented in 36, out of 66, patients with a histological diagnosis of pancreatic duct carcinoma seen from 1991 to 1994. Sixty-six patients with unresectable pancreatic duct carcinoma were separated into two groups. The first group received laparotomy (n=30), with palliative gastric bypass (n=8) or with palliative biliary bypass (n=18). The second group received laparotomy (n=36), with palliative gastric bypass (n=9) or with palliative biliary bypass (n=20), supplemented with locoregional immunostimulation and locoregional chemotherapy. This therapy consisted of ten days of infusion with Proleukin (IL2) and Imukin (gamma-IFN), emulsified in Lipidiol-Urographin. This infusion was performed five days trans-splenically and five days trans-tumorally. Fifteen days later, targeting locoregional chemotherapy was administered, again emulsified in Lipidiol-Urographin. All the patients in the first group died with a mean survival of 5 months. Forty-seven percent (n=17) of the second group achieved a positive objective response, with a mean survival of 14 months. During re-exploration, eight patients became tumor free after pancreatic resection [246].

Miscellaneous drugs

Twenty-nine patients with advanced pancreatic carcinoma (12 patients with liver metastasis at the same time) were randomly divided into two groups. In group A (n=11), patients underwent bilio-enterostomy and/or gastro-enterostomy combined with systemic chemotherapy after surgery. In group B (n=18), patients underwent bilio-enterostomy and/or gastro-enterostomy combined with peripancreatic arterial ligation and arterial infusion regional chemotherapy. Twenty-four patients were followed up for 3-18 months. The palliation of clinical symptoms, changes in carcinoma size by B ultrasound and CT scan, survival period and serum carcinoembryonic antigen (CEA) were observed and compared

between the two groups. Symptoms were alleviated in most patients in group B, and US and CT scan showed that tumor volume decreased in group B. The response rate was 67 percent in group B and 18 percent in group A, which was a significant difference. The mean survival period was 4.8 $\pm$ 0.6 months in group A and 12.5 $\pm$ 1.2 months in group B; i.e. there were significant differences between the two groups. The decrease in serum CEA was 54 percent in group A and 60 percent in group B [247].

There were 80 patients with measurable metastatic or unresectable pancreatic cancer randomly assigned to treatment with either DHAD, VP-16, aclacinomycin, or spirogermanium. There were no complete or partial responses. Two deaths from leukopenia occurred in patients treated with DHAD. One patient receiving spirogermanium experienced a seizure. No other life-threatening toxicities occurred. Maximal toxicities were not significantly more frequent with any treatment group. Median survival was 10 weeks, and median time to progression was only 6 weeks, with no difference among these four therapies [248].

A series of phase II randomized trials were done by the Southwest Oncology Group in which patients with metastatic or advanced pancreatic cancer were randomized to receive single agents (methylglyoxal-bis-guanylhydrazone, MGBG; dihydroxyanthracenedione, DHAD; and aziridinylbenzoquinone, AZQ) or a combined regimen of 5-fluorouracil, doxorubicin, mitomycin C, and streptozotocin, FAM-S. Toxicity, response, and survival were determined. Seventy-one patients received FAM-S and 82, the phase II single agents. Response rates (95 % confidence intervals) for the various treatments were: FAM-S, 11 percent (0 % to 21 %); MGBG, 6 percent (0.8 % to 21 %); DHAD, 0 percent (0 % to 12 %); and AZQ, 0 percent (0 % to 16 %). The median survival times were: FAM-S Group, 5 months and phase II agent group, 3 months. This mean that the FAM-S regimen and the phase II agents tested did not have substantial antitumor activity in pancreatic cancer. The use of new agents as initial therapy is reasonable [249].

One hundred and five patients with advanced measurable pancreatic carcinoma were randomized to receive therapy with maytansine, low-dose chlorozotocin (120 mg/m^2), or high-dose chlorozotocin (175 mg/m^2). Objective response rates were as follows: maytansine, no responses among 48 patients; low-dose chlorozotocin, none among 27; and high-dose chlorozotocin, three among 30 (10 %). Among patients with excellent performance status (Eastern Cooperative Oncology Group grade of 0-1) and no prior chemotherapy, response rates were as follows: maytansine, no responses among 17 patients; low-dose chlorozotocin, none among 14; and high-dose chlorozotocin, three among 28 (11 %). The responses observed with high-dose chlorozotocin were transient (5-8 weeks) and were of no benefit to the patients. None of these agents given by the methods of this study can be recommended for patients with advanced pancreatic cancer [250].

In 1978 was published a study on 66 patients with advanced pancreatic carcinoma that were randomized to receive single agent chemotherapy with either doxorubicin, methotrexate, or actinomycin-D using conventional dose, route and schedule of administration. All patients had measurable lesions which were used to objective assessment of response. For doxorubicin, 2 of 25 patients (8 %) evidenced a partial response (2 of 15 previously untreated patients). One of 25 patients treated with methotrexate and one of 28 received actinomycin-D responded. The duration of responses ranged from 43-64 days for those patients with no chemotherapy prior to study entry. The median survival of patients who received adriamycin as initial treatment was 12 weeks compared to 8 weeks for methotrexate and 6 weeks for actinomycin-D therapy [251].

Cholectokinin receptor antagonist

The effects and safety of loxiglumide, a cholecystokinin-A (CCK-A) receptor antagonist, on advanced pancreatic cancer were investigated in humans. A perspective, controlled (2.4 g/day vs placebo), randomized, double-blind, parallel-group study was performed in 64 patients affected by nonresectable histologically diagnosed pancreatic cancer. The patients were stratified according to gender and stage (A, T3/N0-N1/M0; B, T1-T2-T3/N0-N1/M1; C, relapse after surgical exeresis). Tumor size (by computed tomography scan) and mortality rate were evaluated as efficacy criteria. Clinical symptoms and physical signs, laboratory tests, and adverse reactions were checked every 6 weeks as efficacy/tolerability criteria. Forty-two male and twenty-two female patients were considered. A homogeneous distribution of the patients was demonstrated in the two treatment groups. Group C was not statistically evaluated for survival and tumor evolution because of its small number. Three patients dropped out for causes not related to the therapy. No toxic reactions to the drug were reported. Tumor size monitoring within groups A and B demonstrated a similar increase in both the loxiglumide and the placebo group. Survival in group A was significantly higher than in group B. In group B, survival was significantly lower in females than in males, while survival by gender was similar in group A and in global analysis. Survival by treatment was similar for groups A and B. The tumor grade affected survival but it did not vary by therapy. In conclusion, sure efficacy of loxiglumide in advanced pancreatic cancer was not demonstrated by the results [252].

Gastrin receptor antagonist

Gastrin has been shown to be a growth stimulant in pancreatic cancer cells. Gastrazole is a potent and selective gastrin receptor antagonist. Two randomised blinded trials were conducted to assess the effect of gastrazole in advanced pancreatic cancer. Patients with biopsy-proven, inoperable pancreatic carcinoma were recruited. Trial A compared protracted venous infusion (PVI) gastrazole with PVI placebo, whereas trial B compared PVI gastrazole with PVI 5-fluorouracil. Eighteen patients were randomised in trial A. Gastrazole produced significantly better survival compared to placebo (median 8 months vs 5 months; 1-year survival: 33 vs 11 %, respectively). No difference in toxicity was seen between gastrazole and placebo, except central venous catheter and pump complications. Ninety-eight patients were randomised in trial B. No significant survival difference was detected between gastrazole and 5-FU (median: 3.6 vs 4.2 months; 1-year survival: 13 vs 26 %, respectively). Toxicity of gastrazole was mild with significantly less diarrhoea (p=0.03), stomatitis (p<0.001) and hand-foot syndrome (p<0.001) compared to 5-FU. Quality of life assessment showed similar quality of life between gastrazole and 5-FU at baseline and no significant differences occurred with treatment either between arms or within arms. Compared to placebo, patients with advanced pancreatic cancer treated with gastrazole appeared to live longer, albeit in a very small trial and will require confirmation with large-scale randomised data. However, it did not produce survival advantage over PVI 5-FU [253].

Radiolabelled anti-carcinoembryonic antigen ^{131}I KAb201 antibody

One study aimed to evaluate the safety and tolerability of KAb201, an anti-carcinoembryonic antigen monoclonal antibody, labelled with ^{131}I in pancreatic cancer. Patients with histological/cytological proven inoperable adenocarcinoma of the head of pancreas were randomised to receive KAb 201 via either the intra-arterial or intravenous delivery route. The dose limiting toxicities within each group were determined. Patients were assessed for safety and efficacy and followed up until death. Between 2003 and 2005, 25 patients were enrolled. Nineteen patients were randomised, 9 to the intravenous and 10 to the intra-arterial arms. In the intra-arterial arm, dose limiting toxicity was seen in 2/6 (33 %) patients at 50 mCi whereas in the intravenous arm, dose limiting toxicity was noted in 1/6 patients at 50 mCi,

but did not occur at 75 mCi (0/3).The overall response rate was 6 percent (1/18). Median overall survival was 5 months (95 % confidence interval 3 to 9 months), with no significant difference between the intravenous and intra-arterial arms. One patient was still alive at the time of this analysis. It was concluded that dose limiting toxicity for KAb201 with ^{131}I by the intra-arterial route was 50 mCi, while dose limiting toxicity was not reached in the intravenous arm [254].

Nitrocamptothecin

9-Nitrocamptothecin (9NC) is an orally administered camptothecin analogue that has completed phase III trials for pancreatic cancer. In biological matrices, camptothecin analogues exist in equilibrium between the active-lactone and inactive-hydroxy acid forms. 9NC has been administered on an empty stomach; however, it is unclear if food alters the absorption and disposition of 9NC and its 9-aminocamptothecin (9AC) active-metabolite. Thus, it was evaluated the disposition of 9NC and 9AC after administration of 9NC under fasting conditions and after a standard meal. Patients were randomized to receive 9NC as a single oral dose at 1.5 mg/m^2 with 8 oz of an acidic beverage under fasting conditions, or after a meal consisting of two eggs, 8 oz of orange juice, buttered toast, 8 oz of milk, and 4 oz of hash brown potatoes. Following a 72 h washout period, 9NC was administered with the alternative condition (i.e., with food or fasting). 9NC was then continued for 5 days of every week. Serial blood samples were obtained prior to and from 0.25 to 24 h after administration of 9NC. The total of 9NC and 9AC were measured by an LC-MS/MS assay. It was found that co-administration of 9NC with food reduces the oral absorption of 9NC; however, there was no difference in the exposure of 9AC. The high interpatient variability in the effect of food on the absorption of 9NC and the interpatient variability in the effect of food on the disposition of 9AC is even greater when compared to 9NC [255].

External radiation + drugs

Radiation therapy has been used to improve local control and palliate symptoms in advanced adenocarcinoma of the pancreas. A randomized study was undertaken to determine whether the addition of 5-fluorouracil (5-FU) and mitomycin-C (MMC) to radiation therapy improves outcome in this patient population. One hundred fourteen patients were randomized to receive 59.4 Gy external beam radiotherapy in 1.8 Gy fractions alone or in combination with 5-FU (1,000 mg/m^2/day for 4 days by continuous infusion days 2-5 and 28-31) and MMC (10 mg/m^2 on day 2). One hundred four patients were evaluable for efficacy. Hematologic and nonhematologic toxicities were more common in the combination arm. The response rates were 6 percent in the radiation therapy arm and 9 percent in the combination arm. There were no differences in median disease-free survival time or overall survival time between the combination and radiation therapy alone arms: 5.1 versus 5.0 months, respectively, for disease-free survival time (p=0.19) and 8.4 versus 7.1 months, respectively, for overall survival (p=0.16). The authors concluded that the addition of 5-FU and MMC to radiotherapy increased toxicity without improving survival in patients with locally advanced pancreatic cancer [256].

The objective of one study was to compare the efficacy and toxicity of gemcitabine-based concurrent chemoradiotherapy with paclitaxel-based concurrent chemoradiotherapy in patients with locally advanced pancreatic cancer. A total of 48 patients who had received no prior therapy were enrolled. The patients were treated with 4500 cGy radiation in 25 fractions over 5 weeks concomitant with gemcitabine 1000 mg/m^2/week intravenously and doxifluridine 600 mg/m^2/day/by mouth, or paclitaxel 50 mg/m^2 /week and doxifluridine 600 mg/m^2/day. After a 4-week rest, the responses were evaluated and maintenance therapies (operation or chemotherapy) (gemcitabine 1000 mg/m^2/week and doxifluridine 600 mg/m^2

/day) were conducted. The median survival was 12 months in the gemcitabine group versus 14 months in the paclitaxel group. The response rate was 14 percent versus 25 percent, and the median time to progression was 12 months versus 13 months, respectively. The positive rate of the clinical benefit response was 59 percent versus 42 percent, respectively. Toxicities were acceptable in both groups. In this trial, it was demonstrated that the gemcitabine-based CCRT and the paclitaxel-based CCRT in combination of doxifluridine are clearly acceptable treatment strategy, and appear more effective than the 5 fluorouracil-based CCRT for locally advanced pancreatic cancer with comparable tolerability [257].

To evaluate the effects of the two conformal radiotherapy modalities in the treatment of locally advanced pancreatic carcinoma 1998-2001, 67 patients conformal radiotherapy (CRT). Vacuum cushions were applied to immobilize the patients before contrast CT scans, the treatment plans were simulated by three-dimensional treatment planning system. The patients were randomized into group A to receive a total dose of 45-54 Gy given in 8-12 fractions completed in 18-27 days and group B with a total dose of 45-54 Gy in 15-18 fractions within 20-25 days. The partial and complete pain relief rates of the two groups were 96 percent and 82 percent, respectively, one month after the completion of the radiotherapy, with a median survival of 13 months. The response rates of the patients and the 2-year overall survival rates in group A were 82 percent and 52 percent, respectively, and were 35 percent and 12 percent in group B. The low-dose fractionated radiotherapy was superior than accelerated radiotherapy. For patients with unresectable pancreatic cancer receiving low-dose fractionated CRT, a high dose targeted at the tumor can be given in a fraction and the normal surrounding tissues are exposed to low-dose radiation, to achieve good therapeutic effect with minimized adverse effects on normal tissues in relation to the exposure [258].

Between 1980 and 1984, the American Radiation Therapy Oncology Group conducted a trial in patients with untreated, unresectable localized carcinomas of the pancreas. Patients were randomly chosen to receive either 6,400 cGy with photons, the equivalent dose with a combination of photons and neutrons (mixed-beam irradiation), or neutrons alone. A total of 49 cases were evaluable, of which 23 were treated with photons, 11 with mixed-beam therapy, and 15 with neutrons alone. The median survival time was 6 months with neutrons, 8 months with mixed-beam radiation, and 8 months with photons. The median local control time was 7 months with neutrons, 7 months with mixed-beam radiation, and 3 months with photons. These differences are not statistically significant. Evidence of moderate-to-life-threatening gastrointestinal or hepatic injury was present in three patients treated with neutrons and one patient treated with photons. The authors conclude that the study demonstrates there is no evidence to suggest that neutron irradiation, either alone or in combination with photon irradiation, produces better local control or survival rates than photon irradiation [259].

Randomized trials of the Gastrointestinal Tumor Study Group had previously demonstrated enhanced survival of patients with locally unresectable pancreatic cancer treated with 5-fluorouracil in combination with radiation therapy compared with that of patients treated with radiation therapy alone. In another study it was now compared the survival of patients treated with multidrug chemotherapy (streptozocin, mitomycin, and 5-fluorouracil, SMF) versus radiation combined with 5-fluorouracil followed by the same three-drug SMF combination. In 43 patients randomly allocated between these two arms, an improved median survival for the combined-modality therapy (42 weeks) compared with chemotherapy alone (32 weeks) was demonstrated. Overall survival following this combined-modality treatment program (41 % at 1 year) was significantly superior to that following SMF chemotherapy alone (19 % at 1 year). The authors concluded that for patients with locally unresectable pancreatic adenocarcinoma combined-modality therapy is superior to either optimal radiotherapy or chemotherapy alone [260].

Forty-nine patients with locally advanced carcinoma of the pancreas were treated in a randomized, prospective study comparing definitive helium ion radiation therapy with conventional split-course megavoltage photon irradiation. Patients in each treatment arm underwent exploratory staging laparotomy followed by concurrent radiation therapy and 5-fluorouracil chemotherapy. Patients treated with photons received 6,000 cGy over a period of 10 weeks; patients treated with helium irradiation received a 6,000-7,000-cGy-equivalent dose over a period of 8-9 weeks. There was no significant difference in overall survival between patients in the two treatment arms. Patients treated with helium ions had a slightly longer median survival (8 months) than the photon-treated patients (7 months). Local control rates were slightly higher in the helium-treated patients (10 % vs 5 %). Complications included one chemotherapy-related death. Four of the five helium-treated patients who survived longer than 18 months died of local failure without distant metastases [261].

One hundred fifty-seven patients with locally unresectable pancreatic carcinoma were randomly allocated to therapy with radiation and 5-fluorouracil or radiation and doxorubicin. A total of 138 of 143 analyzable patients have died, and no differences in the relative survival impact of the treatments have been observed. Toxicity on the doxorubicin arm was significantly more substantial and primarily attributable to doxorubicin chemotherapy after the completion of radiotherapy [262].

One hundred and nineteen patients with locally advanced pancreatic cancer, World Health Organization performance status of zero to two were randomly assigned to either the induction CHRT group (60 Gy, 2 Gy/fraction; concomitant 5-fluorouracil infusion, 300 mg/m^2/day, days 1-5 for 6 weeks; cisplatin, 20 mg/m^2/day, days 1-5 during weeks 1 and 5) or the induction gemcitabine group (GEM: 1000 mg/m^2 weekly for 7 weeks). Maintenance gemcitabine (1000 mg/m^2) weekly, 3/4 weeks) was given in both arms until disease progression or toxicity. Overall survival was shorter in the CHRT than in GEM arm (median survival 9 months, 99 % confidence interval 7 to 11, vs 13 months, 99 % confidence interval 9- to 18). One-year survival was, respectively, 32 percent and 53 percent. These results were confirmed in a per-protocol analysis for patients who received 75 percent or more of the planned dose of radiotherapy. More overall grades 3-4 toxic effects were recorded in the CHRT arm, both during induction (36 vs 22 %) and maintenance (32 vs 18 %). It was concluded that the intensive induction schedule of CHRT was more toxic and less effective than gemcitabine alone [263].

> *Summary: Even after many well performed – but mostly rather small – studies during almost three decades the value of radiation with or without cytotoxic drugs have not been sufficiently proven. If there was a substantial effect of radiation it should have been known today.*

IORT

A randomized, controlled trial was conducted to clarify the effect of novel radiosensitizer, PR-350, accompanied by intraoperative radiotherapy (IOR) on locally advanced pancreatic cancer. Between 1999 and 2002, 48 patients were enrolled in a clinical trial and received either PR-350 or placebo. No differences between the PR-350 group (n=22) and control group (n=25) were statically significant. All patients were evaluated, and none of them showed toxicity, with the exception of 1 patient from the control group, and the PR-350 compound was considered to be safe. The efficacy of IOR with PR-350 was evaluated using CT examination. The committee responsible for evaluating efficacy reported that 47 percent of the PR-350 group showed the effective response, compared with 22 percent of the control group (p=0.11). At 6 months following treatment, the tumor mass reduction rate in the PR-350 group was significantly improved. By the time of the last follow-up in 2003, 17 PR-350

patients and 24 control patients group had died of the disease. The median survival period of the PR-350 group was thus 319 days and that of the control group is 303 days. One-year survival rates of the PR-350 group and control group were 37 percent and 32 percent, respectively. Although the PR-350 group did not demonstrate significantly better survival than the control group, four of 22 PR-350 patients were still living more than 2 years after the end of the trial, compared with only one of 25 patients from the control group. The mechanism of this increased therapeutic response to radiotherapy using PR-350 must be clarified to establish more effective strategy for pancreatic cancer treatment [264].

Between 1980 and 1984, 26 patients with resectable adenocarcinoma of the pancreatic head were enrolled in a National Cancer Institute protocol evaluating intraoperative radiotherapy versus standard therapy. After complete excision of their lesions, patients were observed (Stage I), or randomized to intraoperative radiotherapy versus external beam radiotherapy (Stages II-IV). The intraoperative dose was 20 Gy in a single fraction using 9-20 MeV electrons. The external beam radiotherapy schema involved daily 150-180 cGy fractions to 45-55 Gy in 5-6 weeks. Chemotherapy was not used for primary disease but was administered off protocol for recurrent disease. Median potential followup for the trial was > 9 years, with a median patient survival of 18 months. Perioperative mortality was 27% (7 patients). Of the remaining 19 patients, one remains alive and without evidence of disease 9 years post-therapy. Twelve patients underwent autopsy and 2 required antemortem laparotomy; histopathologic evidence of disease recurrence was analyzed. Of 15 patients evaluable for intra-abdominal control, 7 (47 %) suffered local recurrences and 7 (47 %) failed regionally, with 5 patients (35 %) failing in both areas. Five patients (35 %) developed peritoneal seeding. Of 13 patients evaluable for systemic disease, 8 (62 %) suffered distant failure. There were no differences in outcome between intraoperative or external beam radiotherapy or observation in this subset of patients. The authors concluded that it appears clear that advances in local control of this disease are unlikely to translate into increased survival in the absence of improved systemic therapy [265].

In a prospectively randomized trial evaluating pancreatic resection with adjuvant radiotherapy (intraoperative radiotherapy, IORT, vs external beam radiotherapy, EBRT), lymph nodal involvement was examined and correlated with outcome. Twenty-six patients underwent pancreatic resection and received either IORT or EBRT (Stages II-IV). Patients who were stage I received surgery alone. Regional nodal metastases were present in 15 of 26 (57 %) patients. Seven patients suffered treatment-related mortality. Survival, mortality, and morbidity were unaffected by the type of radiotherapy. The survival of patients with negative nodes (median survival 24 months, range 10 to > 109) appeared superior to the survival of patients with nodal involvement (median survival 12 months; range 4-39). Even in patients with locally advanced disease extending into extrapancreatic tissues, two node-negative patients appeared to survive longer (12 and 53 months) than 10 node-positive patients with similarly extensive local disease (median survival 12 months; range 4-39). Local disease control, however, appeared to be independent of nodal involvement, with eventual local recurrences in 6 of 8 node-negative patients and in 4 of 7 node-positive patients who were evaluable for local disease control by autopsy or by antemortem laparotomy [266].

To evaluate whether intraoperative radiation therapy (IORT) results in higher complication rates than conventional radiotherapy, 119 patients were studied who entered four prospectively randomized clinical trials that compared IORT with conventional therapy. Malignant neoplasms included 33 gastric carcinomas, 35 retroperitoneal sarcomas, 22 resectable pancreatic cancers, and 29 unresectable pancreatic cancers. One hundred thirty-six complications developed among 66 patients who received conventional therapy, and 108 complications developed among 53 patients who received IORT. There was no statistical significance between treatment groups with respect to the overall incidence of complications. The overall complication rate associated with IORT was equivalent to conventional

radiotherapy in the treatment of these malignant neoplasms and supported the use of IORT where clinically indicated [267].

> *Summary. So far it has not been shown that IORT is increasing the survival time for the patients. There is still a hope that the local radiation should result in better local control. However, until there is better adjuvant treatment (for liver metastases) available, the possible local benefit of IORT has been difficult to prove.*

A novel sensitizer

Novel hypoxic cell radiosensitiser doranidazole was tested for unresectable pancreatic cancer (locally advanced pancreatic cancer) administered at intraoperative radiotherapy in a placebo-controlled randomised study. Short-term survival was not different. However, a significant difference was observed concerning 3-year survival (doranidazole group vs placebo; 23 % vs 0 %) [268].

Radioactive phosphorous

One prospective randomized trial was undertaken to determine the added efficacy of ^{32}P in treating locally advanced unresectable pancreatic cancer. Thirty patients with biopsy proven locally advanced unresectable adenocarcinoma of the pancreas were assessable after receiving 5-fluorouracil and radiation therapy with or without ^{32}P, followed by gemcitabine. Intratumoral ^{32}P dose was determined by tumor size and volume and was administered at months 0, 1, 2, 6, 7, and 8. Tumor cross-sectional area and liquefaction were determined at intervals by computed tomography scan. Tumor liquefaction occurred in 78 percent of patients receiving ^{32}P and in 8 percent of patients not receiving ^{32}P, although tumor cross-sectional area did not decrease. Serious adverse events occurred significantly more often per patient for patients receiving ^{32}P leading to more hospitalizations. Death was because of disease progression (23 patients), gastrointenstinal hemorrhage (4 patients), and stroke (1 patient). One patient not receiving ^{32}P and one receiving ^{32}P were alive at 28 and 13 months, respectively. ^{32}P did not prolong survival (7 $\pm$ 6 months with ^{32}P vs 12 $\pm$ 8 months without ^{32}P). ^{32}P promoted tumor liquefaction, but did not decrease tumor size. Intratumoral ^{32}P was associated with more serious adverse events and did not improve survival for locally advanced unresectable pancreatic cancer [269].

Brachytherapy

To evaluate the efficacy, toxicity and survival of intraoperative ^{125}I brachytherapy combined with chemotherapy for advanced pancreatic cancer 36 patients with advanced pancreatic cancer were randomized to two groups: brachy-chemotherapy group (n=18) and control group (n=18). For the combined group, intraoperative ^{125}I implantation and gemcitabine, 5-FU was given. For the control group, intratumoral injection of absolute alcohol was done. The complete + partial response rate of brachy-chemotherapy group was 39 percent with pain relief in 78 percent, while that of control group was 0 with pain relief in 22 percent, which is a significant diffrence. Although there were some toxicity in brachy-chemotherapy group, treatment was well tolerated. The 6-, 12-month survival rates of brachy-chemotherapy group were 71 percent and 21 percent and those of control group were 39 percent and 8 percent, respectively. The median survival time was 11 months and 5 months for the two groups, between which the difference was significant. This means that interoperative ^{125}I brachytherapy combined with chemotherapy for advanced pancreatic cancer can control tumor, relieve pain and improve quality of life [270].

Erythropoetin for anemia

Preoperative treatment with 600 U/kg of recombinant human erythropoietin (r-HuEPO) effectively increases erythropoiesis in cancer patients. The aim of this study was to evaluate the erythropoietic response after different doses of r-HuEPO in order to find the minimum effective dose. Twenty anemic sideropenic patients (hemoglobin $\leq$ 110 g/L; serum iron <600 microg/L) with cancer of the gastrointestinal tract were randomly allocated to two groups: the first (n=10) received 400 U/kg of r-Hu EPO divided in 4 doses (100 U/kg each, every 4 days); the second (n=10) received 200 U/kg of r-HuEPO (50 U/kg each, every 4 days). Both groups were given intravenous iron gluconate (125 mg) every day for 15 days. After treatment, the serum iron level significantly rose in both groups. The production of new red blood cells was 176 $\pm$ 91 ml in the 200 U/kg group and 268 $\pm$ 79 ml in the 400 U/kg group, which was a significant difference. The increase of hemoglobin was significantly higher in the 400 U/kg group (22 $\pm$ 2 g/L) than in the 200 U/kg group (14 $\pm$ 3 g/L). It was concluded that the r-HuEPO dose of 400 U/kg appears significantly more effective than the 200 U/kg to stimulate erythropoiesis in anemic sideropenic cancer patients [271].

Regional chemotherapy

It was evaluated the effect of an implanted percutaneous left subclavian artery port-catheter drug delivery system for regional chemotherapy of inoperable pancreatic carcinoma. One hundred and forty patients with inoperable pancreatic carcinoma were enrolled and randomized into two groups to receive the FAM regimen on a 6-day cycle at 1-month intervals: 70 patients in the regional interventional chemotherapy group in which treatment was infused directly into the common hepatic artery, and 70 patients who received the same chemotherapy regimen via the peripheral vein. In the interventional chemotherapy group, there were 5 cases of complete remission (CR) and 49 cases of partial remission (PR), giving a response rate (CR+PR) of 77 percent. Pain control was effective in 96 cases; survival time was in median 14 months. There was no case of CR in the systemic chemotherapy group, and 25 cases of PR, giving a response rate of 36 percent; pain control was effective in 36 percent, and survival time was 1-13 months (median 6 months). The differences between the two groups in response rate and survival were statistically significant. Nausea and vomiting occurred in 49 percent of the interventional chemotherapy group and 41 percent of the systemic chemotherapy group. There were three cases of serious myelosuppression in the systemic chemotherapy group and one patient died. There was a significant difference between the two groups in white blood cell count after the chemotherapy, indicating that the myelosuppressive effect was serious in the systemic chemotherapy group. It was concluded that interventional arterial infusion chemotherapy could significantly improve quality of life and prolong the survival of patients with inoperable pancreatic carcinoma [272].

In an attempt to improve treatment protocols for advanced pancreatic cancer, the value of regional chemotherapy compared with systemic chemotherapy was investigated in this randomized study. Fourteen patients with advanced non-resectable pancreatic adenocarcinoma were randomized receiving either systemic chemotherapy with mitomycin, mitoxanthrone and cisplatin (5 patients) or celiac axis infusion regional chemotherapy with SpherexR microembolization. In the systemic group one patient was stage III, four patients were stage IV, in the intraarterial group two patients were specified stage III and seven were

stage IV. In the systemic group one stable disease and four progressive diseases were noted, in the regional group two stable diseases and seven partial responses were noted. Median survival was 11 weeks in the systemically treated patients versus 33 weeks in the patients treated with intraarterial infusion, which was a significant difference. One patient became resectable (R0). The authors concluded that performance status improved during regional chemotherapy whilst it steadily decreased in the patients treated systemically [273].

Regional intra-arterial infusion chemotherapy (RIAC) has in some instance been valuable to improve prognosis and quality of life of patients with inoperable pancreatic adenocarcinomas, and adjuvant RIAC may play an important role in prolonging survival and reducing risk of liver metastasis after radical resection of pancreatic cancer, but the effect of preoperative or multiple-phase RIAC (preoperative combined with postoperative RIAC) for resectable pancreatic cancers has not been investigated. In one prospective study, the effect of multiple-phase RIAC for patients with resectable pancreatic head adenocarcinoma was evaluated, and its safety and validity comparing with postoperative RIAC were assessed. Patients with resectable pancreatic head cancer were randomly assigned to two groups. Patients in group A (n=50) were treated with new therapeutic mode of extended pancreaticoduodenectomy combined with multiple-phase RIAC, and those in group B (n=50) were treated with extended pancreaticoduodenectomy combined with postoperative RIAC in the same period. The feasibility, compliance and efficiency of the new therapeutic mode were evaluated by tumor size, serum tumor markers, clinical benefit response (CBR), surgical complications, mortality and toxicity of RIAC. The disease-free survival time, median survival time, incidence of liver metastasis, survival rate at 1, 2, 3 and 5 years were also observed. Life curves were generated by the Kaplan-Meier method. The pain relief rate and CBR in group A was 80 and 84 percent, respectively. Serum tumor markers decreased obviously and tumors size decreased in 26 percent of patients after preoperative RIAC in group A. No more surgical complications, mortality or severe systemic side effects were observed in group A compared with group B. The incidence of liver metastasis in group A was 34 percent which was lower than 50 percent in group B. The disease-free survival time and median survival time in group A were 16 months and 18 months respectively. The 1-, 2-, 3- and 5-year survival rates were 55 percent, 35 percent, 25 percent and 13 percent, respectively. There was no significant difference of survival time or survival rates between two groups. The authors concluded that multiple-phase RIAC is effective in combined therapy of resectable pancreatic head carcinomas by enhancing inhibition of tumor growth and reduction of liver metastasis, without negative effect on patients' safety or surgical procedure [274].

The aim of one study was to identify the prognostic factors of a large group of patients with pancreatic cancer who underwent the same regimen of intra-arterial chemotherapy. 5-Fluorouracil (1000 mg/m^2), leucovorin (100 mg/m^2), epirubicin (60 mg/m^2), and carboplatin (300 mg/m^2) were administered every 3 weeks into celiac axis (FLEC regimen). Data of 211 patients with advanced pancreatic cancer who underwent FLEC regimen were analyzed. Eighty-nine had locally advanced disease, and 112 had distant metastases. Median overall survival was 9 months. In both univariate and multivariate analyses, pain reduction after treatment ($\leq$ 30 % of baseline level vs > 30 %; overall survival, 8 vs 12 months), stage of disease (III vs IV; overall survival, 11 vs 7 months), and number of administered cycles ($\geq$ 3 vs >3; overall survival, 6 vs 13 months) were significant and independent predictors of survival. It was concluded that pain reduction, stage of disease, and number of administered cycles are independent prognostic factors of overall survival in a multivariate analysis of patients with advanced pancreatic cancer receiving FLEC regimen intra-arterially [275].

Summary: There is evidence that there are positive effects of intra-arterial chemotherapy in pancreatic cancer. However, the effects are limited, and the treatment is not easy to perform and is expensive. As the topic has been discussed now for at

least 20 years it is probable that – in the ways the technique has been used so far – will never be a routine treatment for advanced pancreatic cancer.

Quality of life

In Lithuania, about 400 cases of pancreatic cancer are diagnosed each year, and more than 50 percent of patients are diagnosed with stage IV disease. Quality of life is an important issue in pancreatic cancer patients. During 2000-2005, two concomitant chemoradiation treatment methods (radiotherapy with 5-fluorouracil and radiotherapy with gemcitabine) were analyzed in the study. A total of 60 patients were enrolled: 41 patients diagnosed with resectable and 19 patients diagnosed with unresectable pancreatic cancer. Quality of life was assessed using European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) questionnaire. Three main quality of life scales (general health status, functional, and symptom scales) were assessed and compared between two treatment groups. The analysis of quality of live assessment showed a statistically significant decrease in quality of life after treatment in patients with resectable pancreatic cancer and treated with radiotherapy and gemcitabine. Decreased quality of life later after treatment was also observed in patients diagnosed with unresectable pancreatic cancer and treated with the same regimen. Treatment with radiotherapy and 5-fluorouracil changed only some aspects of quality of life and did not have a significant impact on quality of life [276].

A phase III trial suggested that a PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen might improve the outcome compared to gemcitabine in advanced pancreatic adenocarcinoma. The analysis of treatment impact on quality of life (QoL) was reported. Patients completed the European Organization for Research and Treatment of Cancer QLQ-C30 and PAN-26 questionnaires at baseline and every second month of treatment until disease progression. The largest differences between arms favored PEFG. Expressed as improvement $\geq$ 10 points from baseline (PEFG/gemcitabine), these were: emotional function (43 vs 18 %), fatigue (41 vs 17 %), QoL (55 vs 29 %), pain (64 vs 41 %), and flatulence (50 vs 26 %). Only change in sexual function favored gemcitabine (19 vs 42 %). Physical function, fatigue, appetite, and satisfaction with healthcare improved in 40-46 percent of partial responders compared with 0-12 percent of patients with stable disease. The authors concluded that clinically relevant improvement in quality of life from baseline was observed more often after PEFG than after gemcitabine. Partial response was associated with improved quality of life suggesting that effective treatment of pancreatic adenocarcinoma may have an important role in these patients [277].

It was analyzed the effect of combined treatment methods on quality of life (QoL) in patients diagnosed with pancreatic cancer. Therefore, it was prospectively analyzed 30 patients with unresectable, without distant metastases, pancreatic cancer. Patients were randomized to 1 of 2 treatment arms: radiotherapy with 5-fluorouracil or radiotherapy with gemcitabine. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire in both treatment groups. QoL was evaluated before and after treatment. It was found that that both concomitant chemoradiation methods have similar impact on QoL in patients with unresectable pancreatic cancer [278].

Cachexia

Data from a clinical study of 86 pancreatic cancer patients with involuntary, significant weight loss (cachexia) were used to explore the relationship between patient-reported outcomes (PROs) and survival. In all, 28 pancreatic cancer patients with cachexia were given gemcitabine (Gemzar) plus 3 mg/kg of infliximab (Remicade), 28 were given gemcitabine

plus 5 mg/kg of infliximab, and 30 were given gemcitabine plus placebo in a double-blinded, phase II, multicenter trial. PRO endpoints included scores from the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Functional Assessment of Anorexia/ Cachexia Therapy (FAACT), Brief Pain Inventory (BPI), and the Short-Form 36 general health survey (SF-36). Population mean scores at baseline indicated fatigue problems (FACIT-F), nutritional health issues (FAACT), and mild-to-moderate pain (BPI "worst pain" score). Baseline normalized SF-36 values for physical functioning, vitality, and mental health indicated substantial impairment. Baseline fatigue and physical-functioning scores predicted survival as well as, or better than, baseline Karnofsky Performance Status or hemoglobin level. A cut-point in the FACIT-F score (median $\leq$ 30) strongly predicted mortality; patients with greater fatigue had a lower median overall survival than did those with less fatigue. These findings supported several features of an a priori clinical-benefit model. Patient-reported fatigue provided powerful prognostic information; tracking of this symptom may be useful for treatment planning and medical monitoring of advanced-stage pancreatic cancer patients with cachexia [279].

Side effects

Diarrhea

Diarrhea is a prominent feature of 5-fluorouracil gastrointestinal toxicity, especially when 5FU is combined with leucovorin or interferon (IFN). No treatment for this condition has been well defined, although drugs, such as diphenoxylate or loperamide, generally are used. The efficacy of octreotide in the treatment of 5FU-induced diarrhea recently has been reported. It was performed a randomized trial that compared octreotide with loperamide, the drug most commonly used for therapy for this disorder. Forty-one patients with grade 2 (four to six stools per day) or grade 3 (seven to nine stools per day; National Cancer Institute toxicity criteria) diarrhea after chemotherapy with a 5FU-containing regimen for colorectal cancer in 28 cases, gastric cancer in six cases, pancreatic cancer in five cases, and breast cancer in two cases, were entered onto the study. Twenty-one patients received octreotide at a dosage of 0.1 mg subcutaneously twice per day for 3 days, and 20 patients received loperamide 4 mg orally initially and then 2 mg every 6 hours for 3 days. The two arms were comparable for age, sex, and primary tumor. Patients were evaluated for response each treatment day; all patients were assessable. Diarrhea resolved significantly in 19 patients in the octreotide arm (one within the first day; four within the second day; and 14 within the third day) versus only three (all after the third day of therapy) in the loperamide arm. Median frequency of stools in the 3 days of therapy was four, three, and zero in the octreotide arm and five, five, and five in the loperamide arm. No side effects were observed in both arms. Ten patients on the loperamide arm and only one on the octreotide arm required hospitalization for parenteral replenishment of fluids and electrolytes. The authors concluded that octreotide seems to be more effective than loperamide in control of diarrhea and elimination of the need for replenishment of fluids and electrolytes [280].

Complications to EGFR inhibitor erlotinib

Data from two large phase III studies were analyzed to characterize the correlation between the occurrence of rash during treatment with the epidermal growth factor receptor inhibitor erlotinib and improved clinical outcomes. Overall survival, progression-free survival (PFS), and tumor response were compared between patients in a rash-evaluable subset who did or did not develop rash in National Cancer Institute of Canada Clinical Trials Group Studies BR.21 (single agent in non-small-cell lung cancer, n=444 in erlotinib group and n=229 in placebo group) and PA.3 (combination with gemcitabine in pancreatic cancer, n=254 in erlotinib plus gemcitabine group and n=245 in placebo plus gemcitabine group). Presence of

rash strongly correlated with overall survival in both studies. In Study BR.21, these correlations increased with rash severity grade: grade 1 versus no rash (hazard ratio, HR, 0.41, p<0.001) and grade $\geq$ 2 versus no rash (HR, 0.29, p<0.001). Similar results were observed for progression-free survival. Disease control (complete response + partial response + stable disease) seemed to increase with the presence and severity of rash. In Study PA.3, grade $\geq$ 2 rash (but not grade 1) strongly correlated with overall survival improvement: grade $\geq$ 2 versus no rash (HR, 0.47, p<0.001). Similarly, grade $\geq$ 2 rash was strongly correlated with improvements in progression-free survival and disease control [281].

Miscellaneously

Ukrain

NSC-631570 (Ukrain) is a semisynthetic compound of thiophosphoric acid and the alkaloid chelidonine from the plant Chelidonium majus. It has been used in complementary herbal medicine for more than 20 years for the treatment of benign and malignant tumors. Between 1999 and 2001, 90 patients with histologically proven unresectable pancreatic cancer were randomized in a monocentric, controlled, randomized study. Patients in arm A received 1000 mg gemcitabine/m^2, those in arm B received 20 mg NSC-631570, and those in arm C received 1000 mg gemcitabine/m^2 followed by 20 mg NSC-631570 weekly. End point of the study was overall survival. In all three arms therapy was well tolerated and toxicity was moderate. At the first re-evaluation in arm A 32 percent, in arm B 75 percent, and in arm C 82 percent showed no change or partial remission according to WHO criteria (arm A vs arm B: p<0.01, arm A vs arm C: p<0.001). Median survival according to Kaplan-Meier analysis was in arm A 5 months, in arm B 8 months, and in arm C 10 months (arm A vs arm B: p<0.01, arm A vs arm C: p<0.01). Actuarial survival rates after 6 months were 26 percent, 65 percent, and 74 percent in arms A B and C, respectively (arm A vs arm B: p<0.05, arm A vs arm C p<0.01). It could thus be show that in unresectable advanced pancreatic cancer, NSC-631570 alone and in combination with gemcitabine nearly doubled the median survival times in patients suffering from advanced pancreatic cancer [282].

The aim of one study was to investigate the effects of Ukrain in the treatment of pancreatic cancer. Most patients with advanced pancreas cancer experience pain and have to limit their daily activities because of tumor-related symptoms. Between 1996 and 1999 42 patients with advanced symptomatic pancreas cancer were randomly assigned to receive either vitamin C (5.4 g every second day, repeated 10 times) and Ukrain (10 mg every second day, repeated 10 times) (21 patients), or vitamin C (5.4 g every second day x 10) and normal saline (10 ml) (control group, 21 patients). The primary measure of efficacy was overall survival. The one-year survival was 81 percent in the Ukrain group compared with 14 percent in the control group. The 2-year survival was 43 percent in the Ukrain group compared with 5 percent in the control group. In a recent study of 126 patients treated with gemcitabine or 5-fluorouracil, none of the patients survived beyond 19 months. The longest survival in the Ukrain group was 54 months after the start of therapy (from March 1996 to date). Median survival was 17 months for Ukrain-treated patients and 7 months for the control group and mean survival was 22 and 9 months for the Ukrain and control groups, respectively, which was a significant difference. Ukrain treatment was well tolerated [283].

Aloe

The recent advances in the analysis of tumor immunobiology suggest the possibility of biologically manipulating the efficacy and toxicity of cancer chemotherapy by endogenous or exogenous immunomodulating substances. Aloe is one of the of the most important plants exhibiting anticancer activity and its antineoplastic property is due to at least three different

mechanisms, based on antiproliferative, immunostimulatory and antioxidant effects. The antiproliferative action is determined by anthracenic and antraquinonic molecules, while the immunostimulating activity is mainly due to acemannan. A study was planned to include 240 patients with metastatic solid tumor who were randomized to receive chemotherapy with or without Aloe. According to tumor histotype and clinical status, lung cancer patients were treated with cisplatin and etoposide or weekly vinorelbine, colorectal cancer patients received oxaliplatin plus 5-fluorouracil (5-FU), gastric cancer patients were treated with weekly 5-FU and pancreatic cancer patients received weekly gemcitabine. Aloe was given orally at 10 ml thrice/daily. The percentage of both objective tumor regressions and disease control was significantly higher in patients concomitantly treated with Aloe than with chemotherapy alone, as well as the percent of 3-year survival patients. The study seems to suggest that Aloe may be successfully associated with chemotherapy to increase its efficacy in terms of both tumor regression rate and survival time [284].

Overall meta-analysis

At the request of the National Thesaurus of Gastrointestinal Cancer (TNCD), the SOR program undertaken by the French Federation of Cancer Centers (FNCLCC) and now led by the French National Cancer Institute (INCa), completed a systematic review to evaluate the value of chemoradiotherapy (CRT) in the management of locally advanced pancreatic adenocarcinoma in collaboration with clinician experts. Results of a systematic literature search using Medline (from 1980 to 2008) were completed by a consult of evidence-based medicine websites. All phase III randomized trials and systematic reviews concerning non resectable locally advanced pancreatic adenocarcinoma and non metastatic (stage III) were included in the study. Some phase II trials were also included if no phase III trials were retrieved. The following interventions were compared: CRT versus best supportive care, CRT versus radiotherapy, and CRT versus chemotherapy. The modalities of CRT regimens and the sequences of chemotherapy-CRT versus CRT were also studied. The quality and clinical relevance of the trials were evaluated using validated checklists, allowing associating each result with a level of evidence. Data synthesis was performed considering both efficacy and toxicity outcomes for each intervention. Nineteen references were included in this systematic review: two meta-analyses, 11 randomized trials, 5 non-randomized trials and 1 randomized trial only published in abstract form. After a clinical and methodological critical appraisal, compared to the alternative BSC, concomitant CRT increases overall survival (C). Concomitant CRT compared to the radiotherapy alone increases the overall survival (B1) but is more toxic (B1). Concomitant CRT compared to chemotherapy alone is not superior in terms of survival (B1) and increases toxicity (A). Concerning administration modalities of radiotherapy, recent data are in favour to a limited irradiation to the tumoral volume (C) and to a total dose of 50-60 Gy in association with 5-FU. The study of radiotherapy associated drugs shows that 5-FU is the reference (B1) and the value of gemcitabine must be proved in randomized trials. Finally, the study of sequences chemotherapy-CRT has recently showed that induction chemotherapy before CRT improves survival (C). Validation of this strategy in a randomized trial is warranted. It was concluded that the use of CRT for locally advanced pancreatic adenocarcinoma is based on a few randomized trials even if this treatment appears superior in terms of survival compared to best supportive care and radiotherapy alone [285].

PAIN RELIEF

Neurolytic coeliac plexus blockade

It was evaluated the pain relieving efficacy, side effects and effects on quality of life of neurolytic coeliac plexus blockade (NCPB) and splanchnic nerves neurolytic blockade (SNB) in body and tail located pancreatic cancer. Patients were randomly divided into two groups. Coeliac group, GC (n=19), were treated with coeliac plexus blockade, whereas the patients in splanchnic group, GS (n=20), were treated with bilateral splanchnic nerve blockade. The VAS values, opioid consumption and quality of life (Patient satisfaction scale=PSS, performance status scale=PS) were evaluated prior to the procedure and at 2 weeks intervals after the procedure with the survival rates. The demographic features were found to be similar. The VAS differences (difference of every control's value with baseline value) in GS were significantly higher than the VAS differences in GC on every control meaning that VAS values in GS decreased more than the VAS values in GC. GS patients were found to decrease the opioid consumption significantly more than GC till the 6th control. GS patients had significant improvement in PS values at the first control. The mean survival rate was found to be significantly lower in GC. Two patients had severe pain during injection in GC and 5 patients had intractable diarrhoea in GC. Comparing the ease, pain relieving efficacy, QOL-effects of the methods, splanchnic nerve blocks may be a good alternative to coeliac plexus blockade in patients with advanced body and tail located pancreatic cancer [286].

There was an additional analysis of data from an earlier reported prospective trial comparing the effect of intraoperative alcohol or saline placebo neurolytic block in patients with pancreatic cancer. The addition was conducted in response to the development of a new theory, which explores the relationship of negative mood states to pain, pain-related behavior, and ultimately, longevity. The original study used a double-blind procedure to randomly assign 139 patients with histologically proven, unresectable pancreatic cancer to receive either an alcohol or a saline block. Data on visual analog pain, mood, and interference with activity were collected preoperatively and every 2 months postoperatively until death. The new analysis was conducted on the complete data sets received from 130 patients. The alcohol intervention had a significant positive effect on life duration and mood scores. High negative mood states correlated significantly with an increase in visual analog pain, the rating of pain intensity at its worse, and pain interference with patients' activities. The authors concluded that in these subjects, the neurolytic block, as compared with medical management alone, improved pain, elevated mood, reduced pain interference with activity, and was associated with an increase in life expectancy [287].

To test the hypothesis that neurolytic celiac plexus block (NCPB) versus opioids alone improves pain relief, QOL, and survival in patients with unresectable pancreatic cancer a double-blind, randomized clinical trial conducted at Mayo Clinic, Rochester. Enrolled (1997 to 2001) were 100 eligible patients with unresectable pancreatic cancer experiencing pain. Patients were followed up for at least 1 year or until death. Patients were randomly assigned to receive either NCPB or systemic analgesic therapy alone with a sham injection. All patients could receive additional opioids managed by a clinician blinded to the treatment assignment. Pain intensity (0-10 numerical rating scale), QOL, opioid consumption and related adverse effects, and survival time were assessed weekly by a blinded observer. Mean (SD) baseline pain was 4.4 (1.7) for NCPB versus 4.1 (1.8) for opioids alone. The first week after randomization, pain intensity and quality of life scores were improved (pain intensity, $p \leq .01$ for both groups; QoL, $p < 0.001$ for both groups), with a significant larger decrease in pain for the NCPB group). From repeated measures analysis, pain was also lower for NCPB over time (P =.01). However, opioid consumption, frequency of opioid adverse effects, and QoL were not significantly different between groups. In the first 6 weeks, fewer NCPB patients reported moderate or severe pain (pain intensity rating of $\geq 5/10$) versus

opioid-only patients (14 % vs 40 %), which was a significant difference. At 1 year, 16 percent of NCPB patients and 6 percent of opioid-only patients were alive. However, survival did not differ significantly between groups. The authors concluded that although neurolytic celiac plexus block improves pain relief in patients with pancreatic cancer vs optimized systemic analgesic therapy alone, it does not affect quality of life or survival [288].

In a randomized double-blind study the efficacy of neurolytic coeliac plexus block (NCPB) was compared with pharmacological therapy in the treatment of pain from pancreatic cancer. Twenty-four patients were divided into two groups: 12 patients underwent NCPB (group 1) and 12 were treated with pharmacological therapy (group 2). Immediate and long-term efficacy, mean analgesic consumption, mortality and morbidity were evaluated at follow-up. Immediately after the block, patients in group 1 reported significant pain relief compared with those in group 2, but long-term results did not differ between the groups. Mean analgesic consumption was lower in group 1. There were no deaths. Complications related to NCPB were transient diarrhoea and hypotension, but not significant between groups. Drug-related adverse effects were constipation (five of 12 patients in group 1 versus 12 of 12 in group 2), nausea and/or vomiting (four of 12 patients in group 1 versus 12 of 12 in group 2) which was significant differences, one gastric ulcer and one gluteal abscess in group 2. The authors concluded that neurolytic coeliac plexus block was associated with a reduction in analgesic drug administration and drug-related adverse effects [289].

Variations and refinements of the classic retrocrural technique of neurolytic celiac plexus block (NCPB) for pancreatic cancer pain have been proposed to improve success rates, avoid complications and enhance diagnostic accuracy. The aim of one prospective, randomized study was to assess the efficacy and morbidity of three posterior percutaneous NCPB techniques in 61 patients with pancreatic cancer pain. The 61 patients were randomly allocated to three NCPB treatment groups: group 1 (20 patients, transaortic plexus block); group 2 (20 patients, classic retrocrural block); and group 3 (21 patients, bilateral chemical splanchnicectomy). The quality and quantity of pain were analyzed before and after NCPB. No statistically significant differences were found among the three techniques in terms of either immediate or up-to-death results. Operative mortality was nil with the three techniques and morbidity negligible. NCPB abolished celiac pain in 70-80 percent of patients immediately after the block and in 60-75 percent until death. Because celiac pain was only a component of the cancer pain in all patients, especially in those with a longer time course until death abolition of such pain did not ensure high percentages of complete pain relief (immediate pain relief in 40-52 %; pain relief until death in 10-24 %). Moreover, NCPB was effective in controlling the pancreatic cancer pain in a higher percentage of cases if performed early after pain onset, when the pain was still only or mainly of celiac type and responded well to nonsteroidal antiinflammatory drug therapy. The probability of patients remaining completely pain-free diminished with increased survival time [290].

The efficacy of neurolytic coeliac plexus block (NCPB) guided by computerized tomography (CT) was compared with pharmacological therapy in the treatment of pain due to pancreatic cancer. The study involved 56 patients who were placed randomly in either a NCPB group or a pharmacological therapy group. At day 1, 7, and 14, the visual analogue scale (VAS) pain scores of the NCPB group were significantly lower than those of the pharmacological therapy group. However, the differences in the improvement of quality of life between two groups were not statistically significant. Moreover, the dose of opioid was significantly lower in the patients of group 1 than those of group 2, while the complications related to NCPB were transient. It was therefore concluded that CT-guided NCPB with alcohol is an effective and safe modality in the management of intractable pancreatic cancer pain [291].

Meta-analysis

The objective of one study was to evaluate the efficacy of EUS-guided celiac plexus neurolysis for pain relief in patients with chronic pancreatitis and pancreatic cancer. An initial search identified 1,439 reference articles, of which 130 relevant articles were selected and reviewed. Data was extracted from 8 studies (n=283) for EUS-guided celiac plexus neurolysis for pain due to pancreatic cancer and nine studies for chronic pancreatitis (n=376) which met the inclusion criteria. With EUS-guided neurolysis, the pooled proportion of patients with pancreatic cancer that showed pain relief was 80 percent (95 % confidence interval 74 to 85). In patients with pain due to chronic pancreatitis, EUS-guided celiac plexus neurolysis provided pain relief in 59 percent (95 % confidence interval 55 to 64). In conclusion, EUS-guided celiac plexus neurolysis offers a safe alternative technique for pain relief in patients with chronic pancreatitis or pancreatic cancer [292].

The aim of one systematic review was to examine the efficacy and safety of neurolytic celiac plexus blockade (NCPB) compared with standard treatment in randomized controlled trials involving patients with unresectable pancreatic cancer. An electronic search was completed (1966 through 2005) for randomized controlled trials comparing NCPB versus control (standard treatment and/or sham NCPB) in patients with unresectable pancreatic cancer. The primary outcome was pain measured on a 10-point visual analogue scale (VAS). Secondary outcomes included opioid usage, adverse effects, quality of life (QOL), and survival. All outcomes were assessed at 2, 4, and 8 weeks. Five randomized trials involving 302 patients (NCPB, n=147; control, n=155) met the inclusion criteria. Compared with control, NCPB was associated with lower VAS scores for pain at 2, 4, and 8 week (weighted mean difference -0.60; 95 % confidence interval -0.82 to -0.37). Opioid usage (in mg/d oral morphine) was also reduced at 2, 4, and 8 week. NCPB was associated with a reduction in constipation (relative risk 0.67; 95 % confidence interval 0.49 to 0.91), but not other adverse events. No differences in survival were observed. QOL could not be adequately analyzed due to differences in outcome scales among studies. It was concluded that patients with unresectable pancreatic cancer, NCPB is associated with improved pain control, and reduced narcotic usage and constipation compared with standard treatment, albeit with minimal clinical significance [293].

> *Summary: Six randomized trials plus two meta-analyses show that for patients with unresectable pancreatic cancer, plexus blockade is associated with improved pain control, and reduced narcotic usage and constipation compared with standard treatment. The impact of the pain relief is limited and the comparisons against peroral morphine are not sufficiently explored with regard to quality of life etc.*

Intraoperative splanchnicectomy

A prospective, randomized, double-blind study was completed comparing intraoperative chemical splanchnicectomy with 50 percent alcohol versus a placebo injection of saline in patients with histologically proven unresectable pancreatic cancer. Standardized assessment of pain, mood, and disability due to pain was completed preoperatively and at 2-month intervals until death. Chemical splanchnicectomy with alcohol was performed in 65 patients, whereas 72 patients received the placebo. The two groups were similar with respect to age, gender, location, and stage of tumor, operation performed, the use of postoperative chemo- and radiation therapy, and initial assessment scores for pain, mood, and disability. No differences in hospital mortality or complications, return to oral intake, or length of hospital stay were observed. Mean pain scores were significantly lower in the alcohol group at 2-, 4-, and 6-month follow-up and at the final assessment. To further determine the effect of chemical splanchnicectomy, patients were stratified into those with and without preoperative pain. In patients without preoperative pain, alcohol significantly reduced pain scores and

delayed or prevented the subsequent onset of pain. In patients with significant preoperative pain, alcohol significantly reduced existing pain. Furthermore, patients with preexisting pain who received alcohol showed a significant improvement in survival when compared with controls. The authors concluded that intraoperative chemical splanchnicectomy with alcohol significantly reduces or prevents pain in patients with unresectable pancreatic cancer [294].

Intrapleural lidocain

The influence of adrenalin on the pharmacokinetics of lidocaine given interpleurally to 10 patients with pancreatic neoplasia was studied. Five patients received an interpleural dose of lidocaine (200 mg; control group), and 5 patients received an interpleural dose of lidocaine (200 mg) plus adrenalin (1:200,000). Plasma and cerebrospinal fluid (CSF) levels of lidocaine were measured before and at specified times (up to 8 hours) after the dose. The analytical technique was radioimmunoassay; and plasma and CSF data were assessed using noncompartmental analysis. The drug was quickly absorbed into the plasma in the control group whereas drug access to CSF was decreased and occurred slowly. The drug was eliminated more quickly from plasma than from CSF, with half-lives of 1.7 $\pm$ 0.4 hours and 3.9 $\pm$ 1.3 hours, respectively. The simultaneous administration of adrenalin delayed absorption. The drug elimination half-lives in plasma and CSF of this group increased to 3.2 $\pm$ 1.2 hours and 8.7 $\pm$ 3.3 hours, respectively. The duration of the analgesia, evaluated as the time until the patient needed another dose, increased from 8.2 $\pm$ 1.5 hours in the control group to 9.7 $\pm$ 1.3 hours in the group that received adrenalin [295].

Octreotide

It was evaluated the analgesic efficacy of a subcutaneous 200 ng bolus of octreotide on somatic and visceral pain from advanced cancer in a randomized, single-blind crossover study. The results in nine cases did not show an analgesic effect superior to that of a placebo. Pain relief was obtained in one case of postprandial visceral pain [296].

NUTRITION

Preventive supplementations

Dietary components may be both causal and protective in cases of pancreatic carcinoma, but the preventive potential of single constituents has not been evaluated. Now it was reported the effects of alpha-tocopherol and beta-carotene supplementations on the rates of incidence of and mortality from pancreatic carcinoma in a randomized, controlled trial. The 29,133 participants in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study were male smokers who were ages 50-69 years at the time they were randomized into 1 of the following 4 intervention groups: dl-alpha-tocopherol (AT; 50 mg/day), beta-carotene (BC; 20 mg/day), both AT and BC, and placebo. The daily supplementation lasted for 5-8 years. Incident cancers were identified through the national Finnish Cancer Registry and death certificates of the Statistics Finland. Effects of both supplementations were statistically nonsignificant. The rate of incidence of pancreatic carcinoma was 25 percent lower for the men who received beta-carotene supplements (n=38) compared with the rate for those who did not receive beta-carotene (n=51) (95 % CI, -51 % to 14 %). Supplementation with alpha-tocopherol (n=51) increased the rate of incidence by 34 percent (95 % CI, -12 % to 105 %) compared with the rate for those who did not receive alpha-tocopherol. Mortality from pancreatic carcinoma during the follow-up, adjusted for stage and anatomic location of the tumor, was 19 percent (95 % CI, -47 % to 26 %) lower among those who received beta-carotene and 11 percent (95 % CI, -28 % to 72 %) higher among those who received alpha-tocopherol as compared with those who did not receive supplementation. The authors concluded that supplementation with beta-carotene or alpha-tocopherol does not have a statistically significant effect on the rate of incidence of pancreatic carcinoma or the rate of mortality caused by this disease [297].

Enzyme supplementation

Impeded flow of pancreatic juice due to mechanical obstruction of the pancreatic duct in patients with cancer of the pancreatic head region causes exocrine pancreatic insufficiency with steatorrhoea and creatorrhoea. This may contribute to the profound weight loss that often occurs in these patients. To investigate whether pancreatic enzyme replacement therapy prevents this weight loss 21 patients with unresectable cancer of the pancreatic head region with suspected pancreatic duct obstruction, a biliary endoprosthesis in situ, and a Karnofsky performance status greater than 60 were recruited to a randomised double blind trial of eight weeks with either placebo or high dose enteric coated pancreatin enzyme supplementation. All patients received dietary counselling. The mean significant difference in the percentage change of body weight was 5 percent (95 % confidence interval for the difference: 0.9 to 8.9). Patients on pancreatic enzymes gained 1.2 percent (0.7 kg) body weight whereas patients on placebo lost 3.7 percent (2.2 kg). The fat absorption coefficient in patients on pancreatic enzymes improved significantly by 12 percent whereas in placebo patients it dropped by 8 percent (95 % confidence interval for the difference: -6 to 45). The daily total energy intake was 8.4 MJ in patients on pancreatic enzymes and 6.7 MJ in placebo patients (95% confidence interval for the difference: 0.08 to 3.44), which was a significant difference. The authors concluded that weight loss in patients with unresectable cancer of the pancreatic head region and occlusion of the pancreatic duct can be prevented, at least for the period immediately after insertion of a biliary endoprosthesis, by high dose enteric coated pancreatin enzyme supplementation in combination with dietary counseling [298].

n-3 fatty acids

n-3 fatty acids, especially eicosapentaenoic acid, may possess anticachectic properties. Therefore a trial compared a protein and energy dense supplement enriched with n-3 fatty acids and antioxidants (experimental: E) with an isocaloric isonitrogenous control supplement (C) for their effects on weight, lean body mass (LBM), dietary intake, and quality of life in cachectic patients with advanced pancreatic cancer. A total of 200 patients (95 E; 105 C) were randomised to consume two cans/day of the E or C supplement (480 ml, 620 kcal, 32 g protein $\pm$ 2.2 g EPA) for eight weeks in a multicentre, randomised, double blind trial. At enrolment, patients' mean rate of weight loss was 3.3 kg/month. Intake of the supplements (E or C) was below the recommended dose (2 cans/day) and averaged 1.4 cans/day. Over eight weeks, patients in both groups stopped losing weight (delta weight E: -0.25 kg/month versus C: -0.37 kg/month; p = 0.74) and lean body mass (delta LBM E: +0.27 kg/month versus C: +0.12 kg/month; p = 0.88) to an equal degree (change from baseline E and C, p<0.001). In view of evident non-compliance in both E and C groups, correlation analyses were undertaken to examine for potential dose-response relationships. E patients demonstrated significant correlations between their supplement intake and weight gain and increase in lean body mass. Such correlations were not statistically significant in C patients. The relationship of supplement intake with change in LBM was significantly different between E and C patients. Increased plasma EPA levels in the E group were significantly associated with weight and LBM gain. Weight gain was associated with significantly improved quality of life only in the E group. Intention to treat group comparisons indicated that at the mean dose taken, enrichment with n-3 fatty acids did not provide a therapeutic advantage and that both supplements were equally effective in arresting weight loss. Post hoc dose-response analysis suggests that if taken in sufficient quantity, only the n-3 fatty acid enriched energy and protein dense supplement results in net gain of weight, lean tissue, and improved quality of life [299].

The aim of a study, in a posthoc analysis, was to examine the effect of dietary compliance on intake and body composition in patients with unresectable pancreatic cancer. Two hundred patients were randomised to receive 2 cans/day of a protein and energy dense, oral nutrition supplement $\pm$ n-3 fatty acids in an international, multi-centre randomised trial over 8 weeks. Dietary compliance was defined a priori as consumption of a minimum of 1.5 cans/day of either supplement. Body composition, dietary intake and quality of life were measured at baseline, 4 and 8 weeks. On average, there were significant differences in energy intake (501 kcal), protein intake (25 g) and weight (1.7 kg) between patients who were compliant with the nutrition prescription compared to noncompliant patients controlling for n-3 fatty acid randomisation, baseline weight and quality of life. Over the 8-week period, there was significant improvement in weight only. There was no significant difference in the energy intake from meals of the total group over the 8 weeks. The authors concluded that compliance with the prescription of 1.5 cans of a protein and energy dense, oral nutrition supplement $\pm$ n-3 fatty acids improved nutrition related outcomes in untreated pancreatic cancer patients. This level of supplement intake did not inhibit meal intake [300].

Lithium gamolenate

Unsaturated fatty acids have an antitumour effect in experimental studies and in phase II studies few side-effects were seen. In this group-sequential, open-label, randomized study, 278 patients with a diagnosis of inoperable pancreatic cancer were treated with either oral (700 mg daily for 15 days), low-dose (0.28 g/kg) or high-dose (0.84 g/kg) intravenous lithium gamolenate (LiGLA). The primary endpoint was survival time from randomization. Median survival after oral and low-dose intravenous treatment was 129 and 121 days respectively. Median survival after high-dose intravenous treatment was 94 days. A good Karnofsky score

and the absence of metastases were associated with increased survival. Haemolysis, a marker of rapid infusion, was associated with a median survival time of 249 days in the low-dose intravenous group. The authors concluded that oral or low-dose intravenous LiGLA led to survival times similar to those of other treatments for pancreatic cancer although one subgroup (low-dose intravenous LiGLA with haemolysis) had longer survival. High-dose intravenous treatment appeared to have an adverse effect [301].

Postoperative nutrition

It was examined the impact of adjuvant total parenteral nutrition after major pancreatic resection for malignancy. A prospective, randomized study was conducted using patients who had undergone a major pancreatic resection with randomization on postoperative day one to either receive or not receive adjuvant total parenteral nutrition. No benefit could be demonstrated by the use of adjuvant parenteral nutrition in this setting. Complications were significantly greater in the group receiving total parenteral nutrition. These complications tended to be those associated with infection. The authors concluded that routine applications of postoperative parenteral nutrition to patients undergoing major pancreatic resection for malignancy cannot be recommended [302].

Immunonutrition

Epidemiologic studies have indicated that high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer. Omega-3 PUFAs in fish oil can inhibit the growth of human cancer cells in vitro and in vivo. These effects are related to the uptake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the cellular substrate pool and their competitive metabolism with arachidonic acid (AA) at the cyclooxygenase and 5-lipoxygenase levels. The metabolites of EPA and DHA have less inflammatory and immunosuppressant potency than the substances derived from AA. Based on previous experimental data, it was hypothesized that fish oil supplementation after major abdominal cancer surgery would improve hepatic and pancreatic function. It was a prospective, randomized, double-blinded clinical trial on 44 patients undergoing elective major abdominal surgery, randomly assigned to receive total parenteral nutrition (TPN) supplemented with either soybean oil (1.0 g/kg body weight daily, n=20) for 5 days or a combination of fish oil and soybean oil (0.2 + 0.8 g/kg body weight daily, respectively, n=24). Compared to pure soybean oil supplementation in the postoperative period, fish oil significantly reduced ASAT (0.8 $\pm$ 0.1 vs 0.5 $\pm$ 0.1 mmol/), ALAT (0.9 $\pm$ 0.1 vs 0.6 $\pm$ 0.1 mmol/), bilirubin (16.1 $\pm$ 5.3 vs 6.9 $\pm$ 0.6 mmol/l), LDH (7.7 $\pm$ 0.4 vs 6.7 $\pm$ 0.4 mmol/) and lipase (0.6 $\pm$ 0.1 vs 0.4 $\pm$ 0.1 micromol) in the postoperative course. Moreover, patients with increased risk of sepsis (IL-6/IL-10 ratio >8) showed a tendency to shorter ICU stay (18 hr) under omega-3 PUFA treatment. Weight loss as encountered after the soybeen oil emulsion of 1.1 $\pm$ 2.2 kg was absent in the fish oil group. This means that after major abdominal tumor surgery, fish oil supplementation improved liver and pancreas function, which might have contributed to the faster recovery of patients [303].

According to international guidelines, artificial nutrition may be indicated after pancreaticoduodenectomy (PD). A clinical study was designed to evaluate whether the route of administration and the composition of the postoperative nutritional support could affect outcome. One hundred patients who underwent pancreaticoduodenectomy for cancer of the pancreatic head were prospectively studied. Patients were randomized to receive a standard enteral formula (SEN; n=35) or immunonutrition with an enteral formula enriched with arginine, omega-3 fatty acids, and RNA (IEN group; n=33), or total parenteral nutrition (TPN; n=32). Postoperative feeding was started within 12 h after surgery. The three regimens were isoenergetic and isonitrogenous. Tolerance of enteral feeding, rate and severity of

postoperative complications, and length of hospital stay (LOS) were evaluated. Full nutritional goal (25 kcal/kg) was achieved in 84 percent of enterally fed patients versus 96 percent in the parenteral group, which was a not significant difference . The rate of postoperative complications was lower in the IEN group (33%) than in the SEN (40 %) and TPN groups (59 %). The severity of infectious complications (sepsis score) was significantly lower in the IEN (5.5) than the SEN (7.9) and TPN groups (10.4). LOS was significantly shorter in the IEN than in the SEN and TPN groups (16.3 vs 17.8 vs 19.3 days, respectively). The authors concluded that in patients undergoing pancreaticoduodenectomy the established nutritional goal can be obtained by enteral feeding, but immunonutrition seems to improve outcome [304].

To evaluate the impact of the route of administration of artificial nutrition and the composition of the diet on outcome a prospective, randomized, clinical trial was performed. One hundred sixty-six consecutive patients undergoing curative surgery for gastric or pancreatic cancer the patients were at operation randomized into three groups to receive: a) a standard enteral formula (control group; n=55); b) the same enteral formula enriched with arginine, RNA, and omega-3 fatty acids (enriched group; n=55); and c) total parenteral nutrition (TPN group; n=56). The three regimens were isocaloric and isonitrogenous. Enteral nutrition was started within 12 hrs following surgery. The infusion rate was progressively increased to reach the nutritional goal (25 kcal/kg/day) on postoperative day 4. Tolerance of enteral feeding, rate and severity of postoperative complications, and length of hospital stay were recorded. Early enteral infusion was well tolerated. Side effects were recorded in 23 percent of the patients, but only 6 percent did not reach the nutritional goal. The enriched group had a significantly lower severity of infection than the parenteral group (4 vs 9). In subgroups of malnourished (n=78) and homologous transfused patients (n=42), the administration of the enriched formula significantly reduced both severity of infection and length of stay compared with the parenteral group. Moreover, in transfused patients, the rate of septic complications was 20 percent in the enriched group, 38 percent in the control group, and 43 percent in the TPN group [305].

The purpose of one study was to determine whether early postoperative enteral feeding with an immune-enhancing formula (IEF) decreases morbidity, mortality, and length of hospital stay in patients with upper gastrointestinal cancer. Between 1994 and 1996, 195 patients with a preoperative diagnosis of esophageal (n=23), gastric (n=75), peripancreatic (n=86), or bile duct (n=11) cancer underwent resection and were randomized to IEF via jejunostomy tube or control. Tube feedings were supplemented with arginine, RNA, and omega-3 fatty acids, begun on postoperative 1, and advanced to a goal of 25 kcal/kg per day. The control involved intravenous crystalloid solutions. Patient demographics, nutritional status, and operative factors were similar between the groups. Caloric intake was 61 percent and 22 percent of goal for the IEF and control groups, respectively. The IEF group received significantly more protein, carbohydrate, lipids and immune-enhancing nutrients than did the control group. There were no significant differences in the number of minor, major, or infectious wound complications between the groups. There was one bowel necrosis associated with IEF requiring reoperation. Hospital mortality was 2.5 percent and median length of hospital stay was 11 days, which was not different between the groups [306].

To investigate the effect of early postoperative enteral nutrition enriched with arginine, RNA and omega-3 fatty acids on immunological and nutritional variables after elective curative operations for gastric or pancreatic cancer a randomised controlled trial with 78 consecutive patients who were to undergo curative operations for gastric or pancreatic cancer, 60 of whom were suitable for the study, was performed. Patients were randomly allocated to three groups (n=20 each) according to the type of postoperative nutritional support: standard enteral diet, the same diet enriched with arginine, RNA, and omega-3 fatty acids or total parenteral nutrition. The daily nutritional goal was 25 kcal (105 kJ)/kg and 0.25 g nitrogen/kg for all patients. All enterally fed patients but one completed the nutritional programme. There

were significant postoperative reductions in both nutritional and immunological variables in all groups. On postoperative days 4 and 8 prealbumin concentration, retinol binding protein (RBP) concentration, delayed hypersensitivity responses, phagocytic ability of monocytes, and concentration of IL-2 receptors had all recovered significantly more in the group receiving the enriched solution. There was no difference in the postoperative infection rates among the three groups, but the infections were significantly less severe in the enriched group [307].

In a randomised controlled study 77 consecutive patients undergoing curative surgery for gastric or pancreatic cancer patients were randomised into 3 groups to receive: a standard enteral formula (n=24); the same formula enriched with arginine, RNA, and omega-3 fatty acids (n=26), isonitrogen isocaloric total parenteral nutrition (n=27). Enteral nutrition was started within 12 h following surgery. Infusion rate was progressively increased reaching the full regimen on postoperative day (POD) 4. On admission and on POD 1 and 8, the following measurements were performed: serum level of total iron-binding capacity, albumin, prealbumin, retinol-binding protein (RBP), and cholinesterase. Delayed hypersensitivity response (DHR), IgG, IgM, IgA, lymphocyte subsets. and monocyte phagocytosis ability were also evaluated. Bioelectrical impedance analysis was performed preoperatively and on POD 2, 7, and 11. In all patients, a significant drop of nutritional and immunologic parameters was observed on POD 1. A significant increase of prealbumin, RBP, monocyte phagocytosis ability, and DHR was found on POD 8 only in the group fed with the enriched diet. A significant reduction of severity of postoperative infections and length of postoperative stay was found in the group with the enriched diet compared to the other groups [308].

The immunomodulating enteral diets are intended to reduce the incidence of postoperative complications in surgical patients. The aim of one study was to assess the clinical effect of such nutrition. Between 2004 and 2007 196 well-nourished patients undergoing resection for pancreatic and gastric cancer were randomized in double-blind manner to receive postoperative enteral nutrition with immunostimulating diet (IMEN group) or standard oligopeptic diet (SEN group). Outcome measures were: number and type of complications, length of hospital stay, mortality, treatment tolerance, liver and kidney function. Finally 183 patients (91 SEN, 92 IMEN group; 69 F, 114 M, median age 61) were analyzed. Median postoperative hospital stay was 12 days in SEN and 13 days in IMEN group. Complications were observed in 21 patients (23 %) in SEN and 23 (25 %) in IMEN group. Four (4 %) patients in SEN group and 4 (4 %) in IMEN had surgical complications. There were no differences in liver and kidney function, visceral protein turnover and treatment tolerance. Results of our study showed no benefit of immunomodulating enteral nutrition over standard enteral nutrition in patients after major gastrointestinal surgery [309].

Summary: There are today seven randomized studies on "immunonutrition", but the results still not seem very robust – it may be shown that there is a positive immuno-modulation, but if this can be translated to survival benefits for the patients or increased quality of life remains to be shown.

TPN versus early enteral nutrition

To evaluate the potential clinical, metabolic, and economic advantages of enteral nutrition over total parenteral nutrition a prospective, randomized clinical trial randomized 257 patients with cancer of the stomach (n=121), pancreas (n=110), or esophagus (n=26) were randomized to receive postoperative total parenteral nutrition (TPN group, n=131) or early enteral nutrition (EEN group, n=126). The nutritional goal was 25 kcal/kg/day. The two nutritional formulas were isocaloric and isonitrogenous, and they were continued until oral intake was at least 800 kcal/day. In 40 consecutive patients, selected nutritional, immunologic and inflammatory variables were studied. Moreover, intestinal oxygen tension

was evaluated by micropolarographic implantable probes. The nutritional goal was reached in 100/126 (79 %) patients in the EEN group and in 128/131 (98 %) patients in the TPN group, which was a significant difference. In the EEN group, hyperglycemia (serum glucose, >200 mg/dL) was observed in 5 percent of the patients versus 9 percent in the TPN group, which was not significant. Alteration of serum electrolyte levels was 4 percent in the EEN group versus 14 percent in the TPN group (p <0.01). No significant difference was found in nutritional, immunologic, and inflammatory variables between the two groups. The overall complication rate was similar (40 % for TPN vs 36 % for EEN). No difference was detected for either infectious or noninfectious complications, length of hospital stay, and mortality. From postoperative day 5, intestinal oxygen tension recovered significant faster in the EEN group than in the TPN group (43 $\pm$ mm Hg vs 31 $\pm$ 4 mm Hg at day 7). EEN was four-fold less expensive than TPN ($25 vs $91/day, respectively) [310].

Direct experimental evidence suggests that total enteral nutrition (TEN) reduces septic morbidity compared with bowel rest and total parenteral nutrition (TPN) and that mucosal support and maintenance of gut barrier function is a key mechanism. This effect is supported indirectly by clinical studies, but this question has not previously been investigated directly in the postoperative patient. One study examined the hypothesis that early enteral feeding after major upper gastrointestinal surgery may modulate gut barrier function and decrease the risk of major infective complications compared with bowel rest and parenteral nutrition. A randomized clinical trial of 67 patients (TPN = 34; TEN = 33) fed postoperatively for 7 days was performed. Thirty-day major morbidity and mortality were monitored. Intestinal permeability was measured using the lactulose/mannitol test preoperatively and on postoperative days 1 and 7. Systemic anti-endotoxin core immunoglobulin G and M antibodies and serum albumin and C-reactive protein were quantified at these time points. No clinical benefit was observed in patients fed enterally compared with the parenterally fed group. Intestinal permeability was increased on the 1st postoperative day in association with evidence of endotoxin exposure. By day 7, enteral feeding compared with parenteral feeding had failed to significantly influence any of the gut barrier or systemic parameters. This randomized controlled trial of TEN vs TPN after major upper gastrointestinal surgery failed to show a clinical benefit for the enteral route. Moreover, enteral nutrition did not modulate gut barrier function postoperatively [311].

Timing of enteral feeding

Delayed gastric emptying occurs in approximately 30 percent of patients after pylorus-preserving pancreatoduodenectomy and causes prolonged hospital stay. Enteral nutrition through a catheter jejunostomy is used to provide postoperative nutritional support. Enteral infusion of fats and proteins activates neurohumoral feedback mechanisms and therefore can potentially impair gastric emptying and prolong postoperative gastroparesis. The effect of a cyclic versus a continuous enteral feeding protocol on postoperative delayed gastric emptying, start of normal diet, and hospital stay was assessed in patients undergoing pylorus-preserving pancreatoduodenectomy. From 1995 to 1996, 72 consecutive patients underwent pylorus-preserving pancreatoduodenectomy. Fifty-seven patients were included and randomized for either continuous (CON) jejunal nutrition (0-24 hr; 1500 kCal/24 hr) or cyclic (CYC) enteral nutrition (6-24 hr; 1125 kCal/18 hr). Both groups had an equal caloric load of 1 kCal/min. On postoperative day 10, plasma cholecystokinin (CCK) levels were measured during both feeding protocols. Nasogastric intubation was 9 days in the CON group (n=30) and 7 days in the CYC group (n=27), which was not statistically significant different. First day of normal diet was significantly earlier for the CYC group (16 vs 12 days). Hospital stay was also significantly shorter in the CYC group (21 vs 18 days). CCK levels were significantly lower in CYC patients, before and after feeding, compared with CON patients. The authors concluded that cyclic enteral feeding after pylorus-preserving pancreatoduodenectomy is associated with a shorter period of enteral nutrition, a faster

return to a normal diet, and a shorter hospital stay. Continuously high CCK levels could be a cause of prolonged time until normal diet is tolerated in patients on continuous enteral nutrition [312].

> *Comment: The study on cyclic enteral feeding is intellectually very interesting, but if it is of clinical value in routine work is stil not known.*

Glutamine

The effect of glutamine (Gln) supplementation in patients undergoing a major operation has not been conclusively established. This study was designed to elucidate the effect of Gln supplementation on the surgical outcome after a pancreaticoduodenectomy (PD) for periampullary tumors. A prospective, randomized, double-blind, and controlled clinical trial was undertaken for patients who underwent a classical PD or a pylorus-preserving PD for periampullary tumors. The Gln and control groups received isonitrogenous amino acid, with a 0.2 g/kg per day Gln regimen administered to the Gln group. The surgical outcome was compared in light of length of postoperative hospital stay, nutritional and chemical profiles, and complication rate between the Gln and control groups. Sixty of the consecutive 143 patients who were admitted to undergo operation for periampullary tumors were enrolled in our study; 32 were in the Gln group and 28 in the control group. The two groups were comparable prior to and during the operation. The median length of the postoperative hospital stay and the postoperative nutritional and chemical profiles were not different between two groups. The overall and PD-related complication rates of the Gln group (38 % and 25 %) and the control group (29 % and 14 %) were not statistically different. Thus, no significant beneficial effect of Gln supplementation with a low-dose parenteral regimen was demonstrated on the surgical outcome after a pancreaticoduodenectomy for periampullary tumors [313].

Growth hormone

Patients with malignancies of the upper GI tract are at increased risk for malnutrition and perioperative death and complications. Standard nutritional support has not significantly altered outcome. Growth hormone (GH) and insulin have been shown to have some benefit in patients with cancer; however, their action in patients undergoing resection has not previously been studied. It was therefore investigated the impact of growth hormone, alone and in combination with insulin, on the protein kinetics of patients with upper gastrointestinal tract cancer who have undergone surgery and were receiving total parenteral nutrition (TPN). Thirty patients undergoing surgery for upper GI tract malignancies were prospectively randomized into one of three nutritional support groups after surgery: 10 patients received standard TPN, 10 received TPN plus daily injections of GH, and 10 received daily GH, systemic insulin, and TPN. The patients underwent a protein kinetic radiotracer study on the fifth day after surgery to determine whole body and skeletal muscle protein kinetics. Patients who received standard TPN only were in a state of negative skeletal muscle protein net balance. Those who received GH and insulin had improved skeletal muscle protein net balance compared with the TPN only group. Whole body protein net balance was improved in the GH and the GH and insulin groups compared with the TPN only group. GH and insulin combined did not improve whole body net balance more than GH alone. GH administration significantly increased serum IGF-1 and GH levels. Insulin infusion significantly increased serum insulin levels and the insulin/glucagon ratio. This means that growth hormone and GH plus insulin regimens improve protein kinetic parameters in patients with upper GI tract cancer who are receiving TPN after undergoing surgery [314].

> *Comment: The study on growth hormone administration postoperatively is also intellectually interesting, but if it is of clinical value in routine work is stil not known.*

Probiotics

Patients undergoing pancreas resection carry several risk factors for nosocomial bacterial infections. Pre- and probiotics (synbiotics) are potentially useful for prevention of these infections. First trials in patients following major abdominal surgery including liver transplantation using one Lactobacillus (LAB) and one fiber showed significant reduction of infection rates and reduced length of antibiotic therapy compared with a control group. One study was designed to analyze whether a combination of different LAB and fibers would further improve outcome. A prospective randomized monocentric double-blind trial was undertaken in 80 patients following pylorus-preserving pancreatoduodenectomy (PPPD). All patients received enteral nutrition immediately postoperatively. One group (A) received a composition of 4 LAB and 4 fibers, and another group (B) received placebo (fibers only) starting the day before surgery and continuing for 8 days. Thirty-day infection rate, length of hospital stay, duration of antibiotic therapy, noninfectious complications, and side effects were recorded. The incidence of postoperative bacterial infections was significantly lower with LAB and fibers (13 %) than with fibers only (40 %). In addition, the duration of antibiotic therapy was significantly shorter in the latter group. Fibers and LAB were well tolerated. It was concluded that early enteral nutrition supplemented with a mixture of LAB and fibers reduces bacterial infection rates and antibiotic therapy following PPPD [315].

Nutrition during radiotherapy

Thirty patients with locally advanced, nonresectable, nonmetastatic cancer in the peripancreatic region, stomach and colorectum-anus, to be treated with radiation therapy with or without adjuvant chemotherapy, were randomized to receive standard diet and either usual between-meal feedings or 300 calories tid of a high nitrogen elemental diet. Although weight loss associated with radiation therapy was not significantly reduced in those receiving the nutritional supplement, delayed hypersensitivity skin test responses tended to improve in patients receiving the elemental dietary supplement and to deteriorate in controls. Planned radiation therapy was completed in all nutritionally supported patients. One control patient expired shortly after treatment was halted abruptly, and three other control patients required rescue by total parenteral nutrition [316].

Thalidomide

Proinflammatory cytokines, especially tumour necrosis factor alpha (TNF-alpha), play a prominent role in the pathogenesis of cancer cachexia. Thalidomide, which is an inhibitor of TNF-alpha synthesis, may represent a novel and rational approach to the treatment of cancer cachexia. A study was now performed to assess the safety and efficacy of thalidomide in attenuating weight loss in patients with cachexia secondary to advanced pancreatic cancer. Fifty patients with advanced pancreatic cancer who had lost at least 10 percent of their body weight were randomised to receive thalidomide 200 mg daily or placebo for 24 weeks in a single centre, double blind, randomised controlled trial. The primary outcome was change in weight and nutritional status. Thirty three patients (16 control, 17 thalidomide) were evaluated at four weeks, and 20 patients (eight control, 12 thalidomide) at eight weeks. At four weeks, patients who received thalidomide had gained on average 0.37 kg in weight and 1.0 cm^3 in arm muscle mass compared with a loss of 2.21 kg (absolute difference -2.59 kg; 95 % confidence interval -4.3 to -0.8) and 4.46 cm^3 (absolute difference -5.6 cm^3; 95 % CI -8.9 to -2.2) in the placebo group, which was statistically significant differences. At eight weeks, patients in the thalidomide group had lost 0.06 kg in weight and 0.5 cm^3 in arm muscle mass compared with a loss of 3.62 kg (absolute difference -3.57 kg; 95 % CI -6.8 to -0.3) and 8.4 cm^3 (absolute difference -7.9 cm^3; 95 % CI -14.0 to -1.8) in the

placebo group which also was significant differences. Improvement in physical functioning correlated positively with weight gain (r = 0.56, p = 0.001). Thalidomide was well tolerated [317].

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