The London Pancreas Workshop

A forum for state-of-the-art clinical and basic research in pancreatic cancer

Friday 28th April 2006
Charterhouse Square, London UK

Final programme

0930-1030: Pancreatic cancer: Diagnostics Chair: Mr Rob Hutchins & Dr Niall Power

Role of CT and MR in pancreatic cancer diagnosis	Dr John Karani, KCH, London
Role of EUS in pancreatic cancer diagnosis	Dr Steve Pereira, UCH, London
Role of staging laparoscopy	Mr Satya Bhattacharya, The Royal London

1030-1100: Coffee Break

11.00-13.00hrs: Pancreatic cancer: Treatment options Chair: Mr Chris Russell & Mr Satya Bhattacharya

Surgery: state of current trials	Dr Paula Ghaneh, Liverpool
Chemotherapy: resected cancer	Prof Claudio Bassi, Verona
Chemotherapy: unresectable cancer	Dr Y Chua, The Royal Marsden
Radiotherapy: what role	Dr Amen Sibtain, St Bartholomew's
Stenting vs surgery for bile duct and duodenum	Dr Colin Ainley, The Royal London
Pain control for unresected tumours	Mr Colin Johnson, Southampton

13.00-14.00hrs: Lunch

14.00-15.00hrs: Pancreatic cancer: Basic science I Chair: Prof Ian Hart & Dr Kairbaan Hodivala-Dilke

Epidemiology and molecular pathology	Prof Jütta Luttges, Saarbucken
Screening in hereditary pancreatitis	Dr Will Greenhalf, Liverpool
Genomics and proteomics	Dr T Crnogorac-Jurcevic, Inst of Cancer
Vaccine development & Gene therapy	Prof Nick Lemoine, Inst of Cancer

15.00-15.30hrs: Tea

15.30-16.30hrs: Pancreatic cancer: Basic science II Chair: Prof Nick Lemoine

Tumour stroma biology	Mr Hemant Kocher, Inst of Cancer
Stellate cell biology	Prof Max Bachem, Ulm
PanIn lesions	Prof Jutta Lüttges, Saarbucken

Organiser: Prof Nick Lemoine & Mr HM Kocher

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Role of CT and MRI in pancreatic cancer diagnosis

Dr John Karani, King's College Hospital, London

Role of EUS in pancreatic cancer diagnosis

Dr Steve Pereira (stephen.pereira@ucl.ac.uk)

The UCL Institute of Hepatology, Royal Free & UCL Medical School, London

Endoscopic ultrasound (EUS) is a sensitive method for detection of pancreatic mass lesions and para-intestinal lymphadenopathy. In conjunction with conventional imaging such as helical computed tomography and magnetic resonance imaging, the indications for EUS include: (i) differentiating between benign and malignant lesions of the mediastinum and upper GI tract, (ii) staging malignant tumours of the lung, oesophagus, stomach and pancreas prior to surgery or oncological treatment, and (iii) assessing suspected mass lesions that are either equivocal or not seen on conventional imaging. In recent years, EUS has charted a course similar to that taken by ERCP, evolving from a purely diagnostic modality to one that is interventional and therapeutic. In pancreatic cancer, these indications include: (iv) obtaining a tissue diagnosis by EUS-guided fine needle aspiration or trucut-type needle biopsy, with an accuracy of greater than 80-90% for the detection of malignancy and a < 1% rate of (generally mild) complications, (v) EUS-guided coeliac plexus neurolysis, and (vi) emerging investigational techniques, which include EUS-guided enteric anastomosis formation and fine-needle injection therapy.

PANCREATIC CANCER: THE ROLE OF STAGING LAPAROSCOPY

S. BHATTACHARYA, The Royal London Hospital

In every pancreatic surgery unit, a proportion of patients whose pancreatic tumours are deemed resectable on pre-operative investigation, are found to have unresectable tumour at the time of laparotomy. In our own practice over the past 5 years, with CT as the principal staging investigation and selective use of Endoscopic Ultrasound (EUS), that figure has been 48 out of 156 patients (31%). The patients who are found to have unresectable disease often undergo a biliary and gastric bypass. However, the same objectives can be achieved by endoscopic biliary stenting and duodenal stenting, without recourse to a laparotomy. It is therefore important that we refine our preoperative staging investigations to try and identify these patients before they come to laparotomy.

The role of pre-operative staging laparoscopy and laparoscopic ultrasound (LUS) has been investigated by several groups (Warshaw et al, Arch Surg 1990; Catheline et al, Surg Endoscopy 1999; Minnard et al, Ann Surg 1998; Andren-Sandberg et al, J Am Coll Surg 1998; Pisters et al, Br J Surg 2001, van Dijkum et al, Ann Surg 2003; McMahon et al, Radiology 2001). Part of the problem with interpreting the literature on this subject is that the quality of the cross-sectional imaging has progressively improved, and it difficult to extrapolate to the present from studies conducted over 5-15 years ago. Secondly, the R0/R1/R2 rates among the patients staged by laparoscopy have not been reported, making it difficult to assess its sensitivity. Moreover, there are few comparisons between EUS and LUS.

The main reasons for an unresectable tumour being discovered at laparotomy are:

1. Small-volume liver metastases not seen on CT/US
2. Small-volume peritoneal deposits not seen on CT/US
3. Vascular involvement (SMA/SMV infiltrated by tumour)
4. Tumour infiltration of the root of the small bowel mesentery

5. Delays in referral, with an interval of several weeks between the scan and the laparotomy (i.e. a more recent scan may have shown irresectability).

Of these, laparoscopy may help identify patients in groups 1, 2 and possibly 4. If LUS is used in addition, it may identify patients in groups 3 and 4.

From my reading of the literature, I would conclude that:

1. There is no justification for routine diagnostic laparoscopy in all patients being staged for pancreatic cancer. All patients should be staged with high quality contrast-enhanced CT.
2. The patients with obvious unresectable disease on CT should not be subjected to surgery/laparoscopy.
3. Patients thought to have resectable disease on the basis of CT can be reasonably subjected to laparotomy, without recourse to laparoscopy.
4. Patients thought to have resectable disease on the basis of CT may be subjected to a diagnostic laparoscopy (ideally combined with LUS) immediately prior to their laparotomy. If this reveals unequivocal liver metastases, peritoneal deposits or bowel mesentery infiltration (preferably confirmed on frozen section), then one should not proceed to laparotomy. If the LUS suggests vascular involvement that would preclude a resection, the decision on whether to proceed to a trial dissection or not would depend on how reliable the surgeon feels those LUS findings are (with a trial dissection being given the benefit of doubt if the findings are equivocal). This entire laparoscopic exercise will prevent a laparotomy in 10-15% of the total number of patients who come to surgery (approximately one-third of the patients with unresectable tumour)

Surgery: state of current trials
Dr Paula Ghaneh, Liverpool

CURRENT STATUS AND TRIALS FOR ADJUVANT TRATMENT AFTER RESECTION FOR PANCREATIC CANCER

Prof. Claudio Bassi, Surgical and Gastroenterological Department, University of Verona – Hospital "G.B. Rossi", 37134 – Verona - ITALY

The only hope for cure in patients with pancreatic tumours is radical resection; in pancreatic cancer survival remains poor with an historical overall 5-year survival rate of only 4%. Although only around 20% of patients are eligible for resection, prognosis is improved in patients who undergo resection with 5-year survival rates of 6-20%. The majority of failures occur within 1-2 years of surgery, either due to local recurrence and/or hepatic metastases.

Despite the enthusiasm in some centers for adjuvant therapy to improve long-term survival, its routine use is not universally established because of inconclusive results from randomized trials available in the literature. A multicenter trial based on a 2x2 factorial design was used to investigate the separate roles of chemoradiotherapy (20Gy in 10 daily fractions over 2 weeks with bolus 500mg/m^2 5-fluorouracil on days 1-3, repeated after 2 weeks) and chemotherapy (bolus 5FU, 425mg/m^2 days 1-5 with folinic acid, 20mg/m^2, monthly for six months) in patients with resected pancreatic ductal adenocarcinoma. Supportive evidence was sought from randomization of additional patients to one or other modality against observation. Of 550 patients randomized, 289 were in the 2x2 factorial design (73 for chemoradiotherapy, 75 for chemotherapy, 72 for both, 69 for observation) and 261 patients were randomized between chemoradiotherapy vs. no chemoradiotherapy (n=69) or between chemotherapy vs. no chemotherapy (n= 192). Analysis was based on 435 (79%) deaths and a median (inter-quartile range) follow-up of 45 (28-64) months. In the 2x2 design the 5-year survival for patients receiving chemoradiation was 10.0% and 19.6% without (χ^2_{LR}=3.75, p=0.053) and 21.1% for patients receiving chemotherapy and 8.4% without (χ^2_{LR}=6.82, p=0.009). Including the additional randomized patients in these analyses further strengthened these results. The chemotherapy benefit remained when adjusting for influential

prognostic factors. This is the largest trial of adjuvant therapy in pancreatic cancer and has shown a strong survival benefit for adjuvant treatment. The standard of care should now be curative resection of pancreatic cancer followed by adjuvant treatment that includes a definitive course of chemotherapy.
These findings have been confirmed in metanalysis setting.

Neoptolemos JP, Stocken DD, Friess H, Bassi C., Dunn JA, Hickey H, Beger H, Fernandez-Cruz L., Dervenis C., Lacaine F., Falconi M., Pederzoli P., Pap A., Spooner D., Kerr DJ Buchler MW; European Study Group for Pancreratic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004,350;1200-1210.

Stocken DD, Buchler MW, Dervenis C, Bassi C, Jeekel H, Klinkenbijl JH, Bakkevold KE, Takada T, Amano H, Neoptolemos JP; Pancreatic Cancer Meta-analysis GroupMeta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005,25:1372-81

Bassi C, Stocken DD, Olah A, Friess H, Buckels J, Hickey H, Dervenis C, Dunn JA, Deakin M, Carter R, Ghaneh P, Neoptolemos JP, Buchler MW; European Study Group for Pancreatic Cancer (ESPAC).
Influence of surgical resection and post-operative complications on survival following adjuvant treatment for pancreatic cancer in the ESPAC-1 randomized controlled trial.
Dig Surg. 2005,22:353-63.

Chemotherapy for unresectable pancreatic cancer

Dr Yu Jo Chua, The Royal Marsden Hospital.

Single agent gemcitabine has been the standard treatment for patients with advanced pancreatic cancer for the past decade, with several previous randomized trials unable to show a benefit for adding other agents to gemcitabine. However, in 2005 the results of two randomized trials were reported, demonstrating an improvement in survival from combining gemcitabine with either the oral 5-fluorouracil prodrug, capecitabine (the UK NCRI GemCap study), or the orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor, erlotinib (the Canadian NCIC-CTG PA.3 study), potentially setting new standards for the palliative treatment of this disease. This presentation will discuss how these developments should inform the management of these patients, as well as the promising treatment combinations which are currently being evaluated in clinical trials.

Radiotherapy in pancreatic cancer: What role?

Amen Sibtain, St Bartholomes's Hospital, London

The role of radiotherapy in pancreatic cancer remains controversial. Judgement on treatment policies is difficult to make because of the lack of studies that unequivocally address the role of radiotherapy. It has been difficult to conduct studies in this group of patients who present late, are often of poor performance status and are few in number. In this respect the ESPAC studies are a huge achievement. However, to recruit a number that was statistically meaningful needed loose randomisation options and there was no quality control for radiotherapy treatment. Ongoing studies will hopefully provide a clearer picture.

The talk will discuss the role of radiotherapy in adjuvant treatment in light of the ESPAC results, outline the data so far on neo-adjuvant treatment and discuss evidence for chemoradiotherapy for inoperable localised tumours.

Radiotherapy treatment is developing in a number of other treatment sites that could also be applied to pancreatic cancer, in particular Intensity Modulated Radiotherapy, The technique allows a greater dose differential between the tumour and normal tissue. This in conjunction with novel molecular or gene based treatments means there may be some hope for more successful treatment outcomes.

Stenting vs surgery for bile duct and duodenum
Dr Colin Ainley, The Royal London Hospital

Many patients with inoperable disease are symptomatic from biliary obstruction requiring either endoscopic stenting or surgical bypass. For biliary stenting plastic and expanding metal stents are available and the metal stents can be either covered or uncovered. Success rates with these three types of stents are similar. The principal complication of stenting is blockage and metal stents are superior to plastic. Attempts to improve plastic stent patency by coating the stent or medication with antibiotics and choleretic agents have been unsuccessful. Covered are superior to uncovered metal stents but have a higher rate of other complications. If required, most covered metal stents can be removed but this is not true for uncovered stents. Cost effectiveness of plastic versus metal stenting relates to patient survival. Trials comparing endoscopic plastic stents with surgery have shown similar technical success rates. Stenting is associated with a lower rate of complications and there is a trend towards a lower 30 day mortality. However, with stenting there is a higher risk of recurrent biliary obstruction and also of duodenal obstruction. There are no trials comparing endoscopic metal stents with surgery.

Some patients also require treatment for duodenal obstruction by endoscopic metal stents or surgical bypass. Both covered and uncovered metal stents can be used with high success rates although covered stents may be superior. There are very few trials but stenting and surgery appear to have similar success and complication rates. However, stenting is associated with early resumption of oral intake and probably improved performance score.

Endoscopic stenting is the treatment of choice for patients with biliary obstruction. Covered expanding metal stents should be used unless there is evidence of advanced disease in which case a plastic stent should be used. Further trials are required to compare stenting with surgery for duodenal obstruction.

Pain control for unresected pancreatic tumours

CD Johnson, Southampton General Hospital

Most patients with upper abdominal malignancy experience severe pain at some time during their illness. Traditionally, opioid analgesia is prescribed to control pain that does not respond to other analgesics. Interruption of pain pathways by celiac plexus block (CPB) or thoracoscopic splanchnicectomy (TS) has been proposed as an opioid-sparing alternative.

Standard medical management (MM) includes escalating doses of non-opioid and then opioid analgesia. The WHO step ladder (1996) envisages progressive treatment with non-opioids, weak opioids and strong opioids, often using slow-release formulations. In addition, MM incorporates adjuvant analgesics such as amitryptilline, valproate and gabapentin, as well as dexamethasone.

A randomised placebo controlled trial of intraoperative CPB showed lower pain scores in the treatment group throughout the follow up. Good pain relief appeared to improve survival. Subsequent studies have confirmed the value of percutaneous CPB in patients not undergoing operation. Approximately 80% of patients experience reduction or abolition of pain.

An alternative approach to achieve visceral denervation is to divide the splanchnic nerves within the chest. Transhiatal splanchnicectomy performed at laparotomy gave over 80% good results[16]. TS avoids the morbidity associated with laparotomy or thoracotomy and in small series has achieved good results with reduced visual analogue pain scores and opioid requirement. However there is no published evidence comparing the effect of TS with either opioid analgesia or CPB, in the treatment of pancreatic malignancy.

In the NaTTS trial these three strategies are offered in a randomized comparison with a strict definition of good pain relief and pain scores measured by daily diaries. Over 60 patients have been recruited from centres in the UK. Interim (blinded) data show that serious adverse events are rare; mortality within 2 months

of randomization is 25%. About half the patients have good pain relief at 2 months. The Data monitoring Committee have recommended that the trial continue, with an increased number of centres.

Pain relief strategies in pancreatic cancer should include escalation of opioid dose and use of adjuvant analgesics if required. Nerve ablation by CPB or TS may offer improved levels of pain relief.

Epidemiology and Molecular Pathology

Prof J.Lüttges, Departement of Pathology, General and Teaching Hospital Saarbrücken, University Homburg/Kiel, Germany

Among the 60 most frequent malignancies pancreatic ductal adenocarcinoma has the most dismal prognosis and causes more than 200.000 deaths worldwide. Incidence rates still equals mortality rates with the highest incidence in western countries. In the different countries however there is a great variability in death rates from 4,2 – 11,5 /100.000 for men and from 2,6 – 7,5 /100.000 for women. There is slight male predominance with 1,1: 1,3. In the years from 1950 to 1980 an increase of death rates was observed worldwide. After 1980 incidence rates were stable in Germany and Austria, whereas in the United States, Canada, Sweden and Australia a slight decrease was observed. A further increase is prognosticated for Southern European countries and Asia after 2006. Pancreatic carcinoma is a disease of the advanced age and rarely occurs below the age of forty. A most important and proven risk factor is cigarette smoking, whereas other factors like coffee consume or alcohol is controversially discussed. Chronic pancreatitis is also an important factor dependent on the background of the pancreatitis. The highest risk was detected for hereditary pancreatitis with 40%. Less than 10% of PDAC have a hereditary background such as FAMMM, Peutz Jeeghers- Syndrom or FAP. At the molecular level sporadic PDAC is characterized by almost 100% mutations for the K-ras gene which was therefore tested as a candidate marker for (early) diagnosis however without convincing results. Other frequent mutation concern p16 and p53 and DPC4. Nowadays diagnostic strategies try to combine the detection of several gene alterations for early diagnosis. Great progress is expected from the evaluation of molecular data from the PanIN lesions.

Screening in Hereditary pancreatitis.

Dr Will Greenhalf, Liverpool

Early identification of pancreatic cancer can allow curative surgery but this is associated with a high morbidity and mortality; the benefits of early diagnosis must therefore be balanced against the consequences of false positive diagnosis. Patients with hereditary pancreatitis are attractive candidates for screening as they have a 40% lifetime risk of pancreatic cancer and, unlike in hereditary cancer syndromes, at-risk individuals within the families are easily identified (on the basis of recurrent attacks of pancreatitis or by testing for known causative mutations). Individuals may develop exocrine and endocrine failure so some of the surgical morbidity is less significant. In addition the surgery may relieve pancreatitis associated pain. However, the morphology of chronic pancreatitis is difficult to distinguish from that of early carcinoma. Total pancreatectomy, the best surgical option to avoid cancer involves greater morbidity than less radical procedures to alleviate the pain of pancreatitis. The 40% lifetime risk is deceptive, as risk increases exponentially with age and the actual probability of cancer is quite low in the periods when patients are most suitable for surgery. A screening program based on CT imaging phased by risk stratification with molecular analysis of pancreatic juice is recommended. Continued research on what clinical or genetic factors may determine which patient will develop cancer is required.

Genomics and Proteomics of Pancreatic Cancer: Discovery of Sperm associated antigen 1 (SPAG1)

Albrecht Neesse, [1#]Rathi Gangeswaran[1#], Jutta Luettges[2], Mark Weeks[1], Nicholas R Lemoine[1] and Tatjana Crnogorac-Jurcevic[1]

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During last several years, we have undertaken large-scale analyses of pancreatic cancer (PDAC) at both gene and protein level, and deciphered complex molecular events underlying the pathobiology of this disease. The aim was to find markers for early diagnosis, when curative surgery is still possible. In addition to analyses of body fluids (blood and urine), detailed functional analysis of several potential early markers is currently ongoing in the laboratory, of which recent data on SPAG1 (Sperm associated antigen 1) will be presented.

SPAG1 was identified in a rare form of infertility where anti-SPAG1 antibodies from the serum of an infertile woman cause sperm agglutination. SPAG1 is known to be expressed in spermatogenesis, but the function of this gene is completely unknown. Finding of overexpression of SPAG-1 in PDAC compared to normal pancreatic tissue was therefore unexpected. With newly generated SPAG1-specific monoclonal antibody we have confirmed the high levels of SPAG1 expression in both testis and PDAC samples, as well as in PanINs (pancreatic intraepithelial neoplasia). Immunocytochemical analysis demonstrated co-localization of SPAG1 with microtubules, and motility assays confirmed the potential role of SPAG1 in cancer cell motility. These findings suggest that SPAG1 could contribute to early spread and consequent poor prognosis of patients with pancreatic adenocarcinoma.

Gene Therapy & Immunotherapy for Pancreatic Cancer

Prof Nick Lemoine, Institute of Cancer, London

While pancreatic cancer remains a deadly disease, the identification of many of the key genetic defects that underlie its pathogenesis has enabled a number of imaginative new strategies for therapy.

For instance, the recognition that cell cycle checkpoint abnormalities are ubiquitous makes pancreatic cancer a target for oncolytic virotherapy using viruses that replicate selectively in cells that have defects in the p53 and Rb signalling pathways. Results of early phase trials using the ONYX 015 adenovirus (a p53-dependent agent) will be reviewed, and preclinical validation studies of the new, more powerful VTP1 adenovirus (an Rb-dependent agent) will be presented.

Genetic prodrug activation therapy is an attractive approach and several clinical trials using different combinations have been conducted in patients with pancreatic cancer. A trial using encapsulated, genetically modified cells implanted peritumorally to activate cyclophosphamide showed safety and some evidence of efficacy in patients with advanced disease. A trial using intra-arterial administration of a retrovirus that activates cyclophosphamide is underway in two centres in the UK presently.

A range of approaches to activate immune recognition and destruction of pancreatic cancer have been explored, including vaccination against mutant oncogene proteins, antibody therapies and cytokine adjuvants. The current status of the field will be reviewed.

Tumour stroma biology

Mr HM Kocher, Centre for Tumour Biology, Institute of Cancer.

Stephen Paget, surgeon at Bart's Hospital, published his seed and soil hypothesis for cancer in 1889. He suggested that the host environment (stroma, distant organs for metastasis) was perhaps as important in cancer progression as the cancer itself. Pancreatic cancer is characterised by marked desmoplastic response. It is unclear whether the cancer cells or the host initiates the fibrosis, though till recently it was believed that the fibrotic response was an innocent by-product of cancer.

With the recent re-surge in interest for stroma as an important player in tumour invasion and metastasis, it has emerged that several of the key growth factors and other cytokines interact with stroma. Pancreatic stellate cells and various matrix proteins and proteoglycans have been implicated in pancreatic tumour progression. Chiefly amongst proteoglycans syndecan, tenascin, decorin and betaglycan have been implicated. Further research in pancreatic cancer stroma needs better in-vitro models to further evaluate this interaction between stroma and cancer cells, in search of novel diagnostic and therapeutic markers.

Pancreatic stellate cell biology

Prof Max G Bachem, Ulm, Germany.

Extensive fibrosis is a hallmark of chronic pancreatitis and of pancreas cancer. Since the first reports on the identification, isolation and characterization of pancreatic stellate cells (PSCs) our knowledge on the development of pancreas fibrosis has grown exponentially. Numerous in vivo and in vitro studies provided strong evidence of a central role for PSC in fibrogenesis associated with acute and chronic pancreatitis and pancreas carcinoma.

PSCs share homologies to hepatic stellate cells (HSC), which have been known to play a major role in liver fibrogenesis for many years. In normal pancreas the fat-storing phenotype of PSCs is found in low numbers (about 4% of the cells) in the periacinar and interlobular space. Similar to the stellate cell activating mechanisms in the liver, also in pancreas injury and pancreas carcinoma stellate cells change their phenotype from the fat-storing to a highly active matrix-producing cell type (activated PSCs). The induction of the activated phenotype of PSC has been shown to involve a number of diverse extra- and intracellular effector molecules, including inflammatory cytokines, growth factors, ethanol, acetaldehyde and oxidative stress. The recent progress in the understanding of the cellular and molecular mechanisms of stellate cell activation and fibrogenesis in the pancreas has led to the development of potential novel treatments for chronic pancreatitis. Probably also the progression of pancreas carcinomas might be delayed by therapeutic strategies targeting stellate cells in pancreas cancer.

Pancreatic Intraepithelial Neoplasia

Prof. J.Lüttges, Departement of Pathology, General and Teaching Hospital Saarbrücken, University of Homburg, Germany

Among the 60 most frequent carcinomas, ductal adenocarcinoma of the pancreas, which is by far the most common tumour type in this gland, remains the one with the worst prognosis. There is still an urgent need to improve the knowledge of early stages of PDAC and thus its early detection. It is presumed that pancreatic ductal carcinomas originate from the epithelium of the duct system, because of their ductal/ductular phenotype. The finding further supports this assumption that hyperplastic and metaplastic changes of the duct epithelium are commonly observed in association with ductal adenocarcinoma. Using microdissection techniques combined with SAGE analysis or DNA CHIP technology it was possible to verify its stepwise development to ductal adenocarcinoma. Morphologically the duct lesions consist of tall columnar epithelium with an increasing papillary folding of the cells and an increase of nuclear atypia. The lesions are classified as **Pan**creatic **I**ntraepithelial **N**eoplasia of three different grades (1A/B, 2 and 3) and the criteria are part of the WHO classification. By SAGE analysis it was shown that a total of 235 genes are differentially expressed in the various PanIN grades. This number was enlarged by the results of microarray hybridisation and expression profiling which detected 1251 genes that were deregulated (multidisciplinary approach of the GPCN (German Pancreatic Cancer Network). According to these differentially expressed genes two major groups of lesions can be divided: a "benign" genotype and a "neoplastic" genotype with the genes found in PanIN3 and manifest ductal carcinoma. It is noteworthy that some genes are up regulated in PanIN2 suggesting an attempt to stop neoplastic transformation.