Genes and surgery in pancreatic cancer
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GENERAL INTRODUCTION
Epidemiology
Periampullary cancer including pancreatic, distal bile duct and ampullary cancer is a dismal disease. The overall 5-year survival after resection ranges from 8% to 21% in pancreatic cancer, 24% to 27% in distal bile duct cancer and 35% to 46% in ampullary cancer. Since more than 60% of periampullary cancers originate from the pancreas, this thesis will be focused mainly on pancreatic cancer despite the fact that some chapters concern different aspects of periampullary cancer.

In the United States, approximately 31,560 newly diagnosed cases of pancreatic cancer and an equal number of deaths will be registered in 2004, making it the fourth leading cause of cancer death in the western world. The peak incidence occurs in the seventh and eighth decades of life, with the average age at diagnosis being 60 to 65 years.

The survival rate of patients with pancreatic cancer is poor. For all stages combined the 1-year survival rate is 19% and the 5-year survival rate is 4%. The 5-year survival rate after resection for pancreatic cancer is 8% in the Academic Medical Center in Amsterdam and 17% in the Johns Hopkins Medical Institutions in Baltimore. Unfortunately, most patients with a pancreatic adenocarcinoma actually are not eligible for surgery, because they present with late-stage disease.

Pancreatic cancer often eludes during its formative stages due to a lack of specific symptoms and limitations in diagnostic methods. Early detection seems to be the key. We therefore need new tests that can diagnose early pancreatic cancers or better yet the precursors to these cancers.

Development
The past decade has witnessed an exponential growth in our understanding of the nature of pancreatic cancer. It is now clear that pancreatic cancer is fundamentally a genetic disease, caused by inherited or acquired mutations in cancer-related genes. With the help of immunohistochemical techniques and a unified nomenclature system to classify the intraductal precursor lesions of pancreatic ductal carcinoma, a histological and genetic progression model has been developed (http://pathology.jhu.edu/pancreas/panin). Similar to the progression in colon cancer from normal epithelium to adenoma to infiltrating carcinoma, pancreatic cancer follows a stepwise development from non-invasive intraepithelial precursor lesions termed pancreatic intraepithelial neoplasms (PanINs) (figure 1).

The histological progression from PanIN-1A (flat) via PanIN-1B (papillary) and PanIN-2 (atypical papillary) to PanIN-3 (severely atypical) has been associated with the simultaneous accumulation of multiple genetic alterations including activating point mutations in the K-ras oncogene, overexpression of Her-2/neu, and inactivation of the p16, p53, DPC4, and BRCA2 tumor-suppressor genes.
Oncogenes

Activating point mutations in the K-ras oncogene are the most common genetic alteration identified in more than 90% of pancreatic ductal cancers. They frequently occur early in the progression from normal duct epithelium to carcinoma. The localization of the majority of K-ras mutations to a single codon makes them relatively easy to detect. This makes K-ras a potential candidate for the development of a molecular-based diagnostic and screening tool for pancreatic cancer. Interestingly, mutant K-ras has been found in patients with chronic pancreatitis as well. Sensitivity and specificity of the different K-ras mutation analyses are not yet well known, which makes their clinical use uncertain.

Tumor suppressor genes

In contrast to the K-ras mutations causing increased functioning in cells, tumor-suppressor genes contribute to carcinogenesis through a loss of function. The p16 gene, located on chromosome 9p, is the most commonly inactivated tumor-suppressor gene in pancreatic cancer. It is inactivated in approximately 95% of pancreatic cancers and can be detected as early as the PanIN-1A stage. p16 inhibits several growth factors leading to a relatively uncontrolled proliferation.

The p53 gene, located on chromosome 17p, is the second most frequently inactivated tumor-suppressor gene in pancreatic cancer. Inactivation of p53 leads to the loss of two important controls of cell growth: regulation of cellular proliferation and the induction of cell death. Despite its frequent intragenetic mutation in pancreatic cancer, inactivation of p53 is a relatively late event in the carcinogenesis that typically occurs when an in situ carcinoma (PanIN-3) becomes invasive.

The DPC4 (deleted in pancreatic cancer locus 4, SMAD4) tumor-suppressor gene, located on chromosome 18q, is mutated or homozygously deleted in approximately 55% of pancreatic
ductal cancers. Like in p53, DPC4 inactivation is a late event in pancreatic carcinogenesis. While expression of DPC4 is present in flat, papillary, or atypical papillary intraductal neoplasms (PanIN-1A, 1B and 2), it is inactivated in approximately 30% of severely atypical intraductal neoplasms (PanIN-3) as demonstrated by immunohistochemical labeling. Loss of DPC4 function inhibits the transforming growth factor-β (TGF-β) pathway, possibly affecting cell growth rate and/or tumor angiogenesis.

Genome maintenance genes

Genome maintenance genes, also known as DNA mismatch repair genes, encode for proteins that check the fidelity of DNA replication. When a genome maintenance gene is dysfunctional due to inactivation, errors that normally occur during DNA replication are not corrected. Mutations in genome maintenance genes can result in a characteristic alteration in tumor DNA called microsatellite instability. Approximately 3% of pancreatic carcinomas display microsatellite instability.

There are two important checkpoints for maintaining chromosome stability. The first is the DNA-damage checkpoint, which prevents cells with DNA damage from entering mitosis. BRCA2 is one of the genes that play a role in DNA-damage checkpoint control implicated in human carcinogenesis. The BRCA2 (breast cancer 2) gene, located on chromosome 13q and frequently inactivated in breast cancer families, is mutated in approximately 7-10% of pancreatic cancers. BRCA2 appears to be an inherited germ-line mutation as opposed to the acquired mutations commonly seen in p16, p53 and DPC4 and it is inactivated late in pancreatic carcinogenesis. Its protein is believed to function as a genomic maintenaince gene by preventing the DNA strands to break, which occurs during normal cell cycle division. The combination of the relatively low incidence and late onset of inactivation of the BRCA2 gene makes it less suitable as a general candidate tumor marker. However, it is conceivable that inactivation of the BRCA2 pathway in a small subset of pancreatic cancers conveys a favorable reaction and responsiveness of these tumors to chemotherapeutic agents known as cross linkers, e.g. mitomycin C.

The second is the spindle checkpoint, which ensures that the chromatids do not separate until they are properly aligned along the mitotic spindle. Abnormalities in spindle checkpoint genes also lead to chromosomal instability. One of the major mechanisms for the generation of chromosomal instability is telomeric dysfunction. Telomeres are structures present at the end of linear chromosomes comprising repeat sequences that prevent fusion between ends of chromosomes. Telomeric fusions between chromosomal arms may occur in the presence of critically shortened telomere repeat sequences.
Identification of new genes
In the past five years the development of new techniques of gene expression profiling has advanced our understanding of pancreatic carcinoma. Serial analysis of gene expression (SAGE) is one of these relatively new techniques which detects the total mRNA expression in samples of interest and obtains a comprehensive profile of cellular gene expression. Neoplastic tissues are compared to non-neoplastic or normal tissues identifying candidate genes that are differentially expressed. Comparisons of SAGE libraries derived from pancreatic carcinomas to SAGE libraries derived from normal pancreatic duct epithelium have identified several genes as highly expressed in pancreatic cancers. Other technologies like cDNA microarrays, oligonucleotide arrays, and proteomics have advanced our understanding of pancreatic cancer. All these global gene expression methods have revealed an enormous amount of information providing novel insight into the biology of pancreatic cancer, which serves to generate new studies.

Diagnosis and staging
The early symptoms of pancreatic cancer are nonspecific and become usually only specific after invasion or obstruction of a nearby structure. Obstruction of the biliary tree resulting in jaundice is the most common initial physical finding in pancreatic head carcinoma. Laboratory studies show the accompanying nonspecific elevated serum bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase. The most extensively studied tumor marker CA19-9 has proven not to be useful as diagnostic marker, but rather as marker for tumor recurrence.

In most hospitals spiral computed tomography (CT) is the primary imaging study for patients with suspected periampullary cancer. Its sensitivity ranges from 85% to 95% and approaches 100% for lesions larger than 15 mm. Yet maximal benefit of surgical resection is to be expected in patients with small lesions. For early detection, endoscopic ultrasonography (EUS) with or without fine-needle aspiration (FNA) may be the imaging modality of choice because it detects smaller pancreatic lesions. The finding of a combination of strictures in the extrahepatic biliary duct and the pancreatic duct (double duct sign) at endoscopic retrograde cholangiopancreatography (ERCP) is virtually pathognomonic for pancreatic adenocarcinoma. Moreover, cytologic specimens can be obtained by brushing the distal bile duct during ERCP, which might help to differentiate between malignant and benign lesions. Although magnetic resonance imaging (MRI) offers no advantage over CT, the introduction of MR-choangiopancreatography (MRCP) makes it possible to visualize both the bile duct and pancreatic duct. Diagnostic laparoscopy appears to provide little additional information and is not warranted in patients who would benefit from palliative surgery if unresectable.

An accurate tissue diagnosis is helpful in determining the treatment strategy in patients with suspected pancreatic cancer. With the introduction of EUS-guided FNA an advance in tissue
sampling has been notable. The sensitivity and specificity of EUS-guided FNA for the diagnosis of adenocarcinoma ranges from 75% to 94% and from 50% to 100%, respectively, with a diagnostic accuracy between 86% and 94%.\textsuperscript{43} This variable and low sensitivity possibly caused by inadequate sampling of the lesion impedes the diagnostic process. ERCP is another valuable method for obtaining cytology by brushing an undiagnosed bile duct stricture in order to differentiate malignant from benign lesions. Although the specificity of brush cytology for detecting malignant stenoses is up to 95%, its sensitivity remains low between 35% and 40%.\textsuperscript{19}

Analysis of the obtained cytology for the known molecular changes occurring stepwise in the progression from normal epithelium to carcinoma may improve the sensitivity for the diagnosis of periampullary malignancies. K-ras codon 12 point mutations have been widely studied in cytology samples, pancreatic juice and serum. Several studies have found that K-ras mutation analysis may help to differentiate between malignant and benign lesions and is more accurate than cytology alone.\textsuperscript{44,46} Unfortunately, mutant K-ras is also found in patients with chronic pancreatitis without pancreatic cancer, and thus the specificity of K-ras analysis for an accurate diagnosis of neoplastic disease remains a concern. However, a long follow-up period may be needed to determine the true significance of these K-ras mutations found in patients without obvious neoplastic disease. Several techniques for the detection of K-ras mutations have been developed in other cancers. The novel amplification refractory mutation system (ARMS) assay is a quantitative test for K-ras mutations and potentially should yield a specificity of a 100%.\textsuperscript{47}

Combining K-ras analysis with \textit{P16}, \textit{P53} and \textit{DPC4} will hopefully allow higher specificity without loss of sensitivity. Immunohistochemical analysis for proteins of genes mutated early in pancreatic cancer may be of value, particularly if combined with immunohistochemical analysis of other protein products. Immunohistochemistry for the \textit{DPC4} protein showed that loss of expression is specific for the diagnosis of pancreatic and bile duct cancer.\textsuperscript{48}

Resection

In 1912 Kausch reported the first successful resection of a portion of the pancreas and the duodenum for an ampullary cancer.\textsuperscript{49} In 1935 Whipple and colleagues reported the first three pancreaticoduodenectomies. Surgical resection has since offered the only chance for cure in patients with periampullary cancer.\textsuperscript{1,50} Although Kausch and Whipple described the pancreaticoduodenectomy with sparing of the pylorus and the entire stomach, in the 1970s pancreaticoduodenectomy was most commonly performed in combination with a distal gastrectomy. In 1978 Traverso and Longmire repopularized the concept of pylorus preservation during pancreaticoduodenectomy (figure 2).\textsuperscript{2,51}

Today this is still the operation of choice in most periampullary cancers including pancreatic, distal bile duct and ampullary cancer. However, preoperative differentiation between benign
and malignant lesions is often difficult, while this distinction might have implications for the optimal treatment strategy. For example, (non-invasive) ampullary adenomas should preferably be treated with local resection. Controversy currently exists whether the "suspicous for cancer" adenomas or early pT1 carcinomas can be adequately treated by local resection or should be treated by a pancreaticoduodenectomy.

Centralization
Given the small number of long-term survivors after resection for periampullary cancer, minimization of surgery-related morbidity and mortality is imperative. Reported morbidity after pancreatic resection remains substantial with percentages in literature between 30% and 50%. Although once associated with high operative mortality, pancreatic resection can now be performed relatively safely at several centers with reported 5-year survival rates up to 40%. However, hospital mortality rates after pancreatic resection still differ considerably in statewide and nationwide surveys. In large series from specialized centers mortality rates vary between 0% and 4%. These figures are in sharp contrast with a large survey from the UK that revealed a mortality rate of 28% in a 10-year period. Inverse relationships between hospital volume and mortality have long been recognized and are strongest in high-risk surgical procedures such as pancreatic resection. The "practice makes perfect" hypothesis originally proposed by Luft et al. in 1979 seems to remain valid, but it is difficult to demonstrate since evidence is hard to get. The only way to get unbiased data on mortality rates is to keep up all patients undergoing a pancreatic resection in an independent nationwide registry.
Palliation

At the time of clinical presentation approximately 80% of patients are not eligible for surgical resection because of local spread or metastatic disease found during diagnostic work-up. In case of unresectability appropriate palliation of the major symptoms including jaundice, duodenal obstruction and pain is of utmost importance. Both surgical and non-surgical strategies can be used for the relief of mentioned symptoms, but no consensus has been reached on which strategy should preferably be used, nor the criteria for selection of the patients for either treatment are known.

Around 70% of the patients diagnosed with pancreatic cancer suffer from obstructive jaundice. If left untreated, this can result in progressive liver failure and early death. Biliary decompression can be achieved by non-surgical intervention with endoscopic or percutaneous transhepatic techniques, or by surgical intervention. The short-term success rate of non-surgical intervention in term of relief of the biliary obstruction varies between 82% and 100%. However, stent obstruction and cholangitis are seen in up to 20% to 50% of the patients who survive longer than 6 months. In most studies, a surgical intervention by means of a bypass is associated with higher mortality and morbidity rates, but less recurrent obstructive jaundice during follow-up. Since the development of endoscopic techniques is still ongoing, the choice between non-surgical and surgical management of jaundice remains under discussion.

The very same discussion as in biliary obstruction accounts for the treatment options in patients with duodenal obstruction. Approximately 10-20% of patients with advanced pancreatic cancer develop duodenal obstruction at some point before death. In several studies a correlation is found between survival and the development of duodenal obstruction: the longer the survival, the higher the rate of duodenal obstruction.

Figure 3  Double bypass consisting of a hepaticojejunostomy and a prophylactic gastrojejunostomy (with permission - © S.M.M. de Castro)
Pain is present in 30-40% of patients presenting with unresectable pancreatic cancer and increases to 90% shortly before death. Untreated pain significantly affects quality of life in most of these patients. Therefore, several studies have been performed addressing the different options for pain relief, for example intraoperative chemical splanchnicectomy.

Of the patients with periampullary tumors who undergo an exploratory laparotomy with the intention to perform a pancreaticoduodenectomy, still 25% to 75% prove to have unresectable disease. At that stage the obvious means for palliation of obstructive jaundice is operative biliary decompression by some form of surgical bypass, e.g., a hepaticojejunostomy. The advice following a randomized controlled trial performed at the Johns Hopkins Medical Institutions in 1999 was to perform a prophylactic gastrojejunostomy routinely in patients with periampullary cancer found to be unresectable during laparotomy. Nevertheless, controversy still exists in general surgical practice if a double bypass should be performed routinely in these patients (figure 3).


