Pancreas Cancer

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the pancreas cancer.
[Smith MH. **Pancreas Cancer.** *Cancer Biology* 2013;3(3):83-147]. (ISSN: 2150-1041). http://www.cancerbio.net. 4

Keywords: cancer; biology; life; disease; research; literature; pancreas

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Adell, T., A. Gomez-Cuadrado, et al. (2000). "Role of the basic helix-loop-helix transcription factor p48 in the differentiation phenotype of exocrine pancreas cancer cells." Cell Growth Differ **11**(3): 137-47.

The majority of human pancreatic adenocarcinomas display a ductal phenotype; experimental studies indicate that tumors with this phenotype can arise from both acinar and ductal cells. In normal pancreas acinar cells, the pancreas transcription factor 1 transcriptional complex is required for gene expression. Pancreas transcription factor 1 is a heterooligomer of pancreas-specific (p48) and ubiquitous (p75/E2A and p64/HEB) basic helix-loop-helix proteins. We have examined the role of p48 in the phenotype of azaserine-induced rat DSL6 tumors and cancers of the human exocrine pancreas. Serially transplanted acinar DSL6 tumors express p48 whereas DSL6-derived cell lines, and the tumors induced by them, display a ductal phenotype and lack p48. In human pancreas cancer cell lines and tissues, p48 is present in acinar tumors but not in ductal tumors. Transfection of ductal pancreas cancers with p48 cDNA did not activate the expression of amylase nor a reporter gene under the control of the rat elastase promoter. In some cell lines, p48 was detected in the nucleus whereas in others it was cytoplasmic, as in one human acinar tumor. Together with prior work, our findings indicate that p48 is associated with the acinar phenotype of exocrine pancreas cancers and it is necessary, but not sufficient, for the expression of the acinar phenotype.

Adsay, N. V., O. Basturk, et al. (2004). "Pancreatic pseudotumors: non-neoplastic solid lesions of the pancreas that clinically mimic pancreas cancer." Semin Diagn Pathol **21**(4): 260-7.

In the pancreas, a variety of non-neoplastic conditions may form solid masses that may mimic cancer. Up to 5% of pancreatectomies performed with the preoperative clinical diagnosis of carcinoma will prove to be non-neoplastic by pathologic examination, although this figure is decreasing with improved diagnostic modalities. Chronic inflammatory lesions are the leading cause of this phenomenon ("pseudotumoral pancreatitis"), and among these, autoimmune and paraduodenal pancreatitides (discussed separately in this issue) are most important. In this article, we will focus on the noninflammatory lesions that may form tumor-like lesions of the pancreas. Adenomyomatous hyperplasia of ampulla of Vater is a subtle lesion that is difficult to define; larger examples (>5 mm) have been found to be the cause of obstructive jaundice. Accessory (heterotopic) spleen may form a well-defined nodule within the tail of the pancreas and is typically mistaken for endocrine neoplasm. Lipomatous hypertrophy is the replacement of pancreatic tissue with mature adipose tissue that occasionally leads to moderate to marked enlargement of the pancreas. Hamartomas are very rare if the entity is defined strictly. They are characterized by irregularly arranged mature pancreatic elements admixed with stromal tissue. A cellular, spindle-cell variant with c-kit (CD117) expression is recognized. Pseudolymphoma forms well-defined nodules composed of hyperplastic lymphoid tissue. Rarely, foreign-body deposits, granulomatous inflammations (such as sarcoidosis or tuberculosis), and congenital lesions may form tumoral lesions. In conclusion, it is

important to recognize the types of conditions that form pseudotumors in the pancreas so that they can be distinguished from ductal adenocarcinomas, especially clinically, but also pathologically. Nonspecific terms such as "inflammatory pseudotumor" ought to be avoided, and every attempt should be made to classify a "pseudotumor" into a more specific diagnostic category discussed above.

Agrawal, S., E. R. Kandimalla, et al. (2002). "GEM 231, a second-generation antisense agent complementary to protein kinase A RIalpha subunit, potentiates antitumor activity of irinotecan in human colon, pancreas, prostate and lung cancer xenografts." Int J Oncol **21**(1): 65-72.

GEM 231, a second-generation antisense oligonucleotide targeted against the RIalpha subunit of protein kinase A (PKA) was co-administered with the chemotherapeutic agent irinotecan, a topoisomerase-I inhibitor, to study the antitumor efficacy of the combination in nude mice bearing various human tumor xenografts. The combination treatment of GEM 231 and irinotecan produced enhanced and prolonged tumor-growth inhibition, compared with irinotecan monotherapy, against human colon (HCT-116), pancreas (Panc-1), prostate (PC3) and lung (SKMES) tumors in mice. The extent of tumor-growth inhibition, however, varied among the different tumor models studied. The tumor-growth inhibition depended on the dose of GEM 231 co-administered with irinotecan. The combination of GEM 231 (20 mg/kg, i.p., 5 days on 2 days off x 7) and irinotecan (50 mg/kg, i.v., qwk x 3) produced significantly longer tumor-growth delay than did irinotecan administered alone. Importantly, the co-administration of irinotecan and GEM 231 did not result in higher toxicity compared with monotherapies in the several tumor models tested. These results suggest that the use of irinotecan in combination with GEM 231 may increase the therapeutic index of irinotecan in cancer patients.

Aguilar, S., J. M. Corominas, et al. (2004). "Tissue plasminogen activator in murine exocrine pancreas cancer: selective expression in ductal tumors and contribution to cancer progression." Am J Pathol **165**(4): 1129-39.

Tissue plasminogen activator (tPA) is absent from normal human pancreas and is expressed in 95% of human pancreatic adenocarcinomas. We have analyzed the expression of components of the tPA system in murine pancreatic tumors and the role of tPA in neoplastic progression. Transgenic mice expressing T antigen and c-myc under the control of the elastase promoter (Ela1-TAg and Ela1-myc, respectively) were used. tPA was undetectable in normal pancreas, acinar dysplasia, ductal complexes, and in all acinar tumors. By contrast, it was consistently detected in Ela1-myc tumors showing ductal differentiation. Crossing transgenic Ela1-myc with tPA-/- mice had no effect on the proportion of ductal tumors, indicating that tPA is not involved in the acinar-to-ductal transition. Ela1-myc:tPA-/- mice showed an increased survival in comparison to control mice. All ductal tumors, and none of the acinar tumors, overexpressed the tPA receptor annexin A2, suggesting its participation in the effects mediated by tPA. Our findings indicate that murine and human pancreatic ductal tumors share molecular alterations in the tPA system that may play a role in tumor progression.

Algul, H., M. Treiber, et al. (2007). "Mechanisms of disease: chronic inflammation and cancer in the pancreas--a potential role for pancreatic stellate cells?" Nat Clin Pract Gastroenterol Hepatol **4**(8): 454-62.

Late diagnosis and ineffective therapeutic options mean that pancreatic ductal adenocarcinoma (PDA) is one of the most lethal forms of human cancer. The identification of genetic alterations facilitated the launch of the Pancreatic Intraepithelial Neoplasm nomenclature, a standardized classification system for pancreatic duct lesions, but the factors that contribute to the development of such lesions and their progression to high-grade neoplasia remain obscure. Age, smoking, obesity and diabetes confer increased risk of PDA, and the presence of chronic pancreatitis is a consistent risk factor for pancreatic cancer. It is hypothesized that chronic inflammation generates a microenvironment that contributes to malignant transformation in the pancreas, as is known to occur in other organs. Pancreatic stellate cells (PSCs) are the main mediator of fibrogenesis during chronic pancreatitis, but their contribution to the development of PDA has not been elucidated. Data now suggest that PSCs might assume a linking role in inflammation-associated carcinogenesis through their ability to communicate with inflammatory cells, acinar cells, and pancreatic cancer cells in a complicated network of interactions. In this Review, the role of PSCs in the process of inflammation-associated carcinogenesis is discussed and new potential treatment options evaluated.

Antwi, K., P. D. Hanavan, et al. (2009). "Proteomic identification of an MHC-binding peptidome from pancreas and breast cancer cell lines." Mol Immunol **46**(15): 2931-7.

Peptides bound to cell surface MHC class I molecules allow the immune system to recognize intracellular pathogens and tumor-derived peptides. Our goal was to learn what the immune system "sees"

on the surfaces of tumor cells by acid-eluting peptides from HLA molecules for extended time periods. We determined how long peptides would continue to elute over time from a pancreatic tumor cell line, Panc-1, and a breast cancer cell line, MCF-7, at pH 3.0 in citrate buffer while monitoring viability. Both cell lines demonstrated greater than 90% viability after 25min at pH 3.0. Panc-1 remained >90% intact after 45min at pH 3.0. Acid eluted peptide sequences were identified using LC-MS/MS and searching the NCBI refseq database. The total number of peptides eluted peaked between 40 and 45min for Panc-1, but continued to increase over time from MCF-7. A total of 131 peptides were identified from Panc-1 while 101 peptides were identified from MCF-7 elutions. Two classes of peptides were eluted: (1) 8-10 amino acid peptides fitting the HLA-binding motifs of each cell line, and (2) peptides longer than 10 amino acids containing HLA-binding motifs of each cell line. W6/32 antibody affinity purification of intact MHC molecules after papain cleavage of MHC class I from tumor cell surfaces also indicated that peptides longer than 10 amino acids bind to class I proteins. A peptide-MHC-refolding assay further substantiated the binding of longer peptides to HLA-A*0201. Our findings provide sequences and gene names of peptides presented by MHC class I molecules from common pancreas and breast cancer cell lines. We utilized a novel refolding assay to demonstrate that peptides longer than the canonical 8-10 amino acids commonly bind in MHC class I cell surface molecules.

Antwi, K., G. Hostetter, et al. (2009). "Analysis of the plasma peptidome from pancreas cancer patients connects a peptide in plasma to overexpression of the parent protein in tumors." J Proteome Res **8**(10): 4722-31.

Blood circulates through nearly every organ including tumors. Therefore, plasma is a logical source to search for tumor-derived proteins and peptides. The challenge with plasma is that it is a complex bodily fluid composed of high concentrations of normal host proteins that obscure identification of tumor-derived molecules. To simplify plasma, we examined a low molecular weight (LMW) fraction (plasma peptidome) using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. In the plasma peptidome of patients with ductal adenocarcinoma of the pancreas (DAP), a prominent peptide was identified from the QSOX1 parent protein. This peptide is stable in whole blood over 24 h and was present in 16 of 23 DAP patients and 4 of 5 patients with intraductal papillary mucinous neoplasm (IPMN). QSOX1 peptides were never identified in the plasma peptidome from 42 normal healthy donors using the same methods. Immunohistochemical staining of DAP tissue sections with anti-QSOX1 antibody shows overexpression of QSOX1 in tumor but not in adjacent stroma or normal ducts. Three of four pancreas tumor cell lines also express QSOX1 protein by Western blot analysis. This is the first report of QSOX1 peptides in plasma from DAP patients and makes the rare connection between a peptide in plasma from cancer patients and overexpression of the parent protein in tumors.

Argani, P., C. Iacobuzio-Donahue, et al. (2001). "Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE)." Clin Cancer Res **7**(12): 3862-8.

PURPOSE: Effective new markers of pancreatic carcinoma are urgently needed. In a previous analysis of gene expression in pancreatic adenocarcinoma using serial analysis of gene expression (SAGE), we found that the tag for the mesothelin mRNA transcript was present in seven of eight SAGE libraries derived from pancreatic carcinomas but not in the two SAGE libraries derived from normal pancreatic duct epithelial cells. In this study, we evaluate the potential utility of mesothelin as a tumor marker for pancreatic adenocarcinoma. EXPERIMENTAL DESIGN: Mesothelin mRNA expression was evaluated in pancreatic adenocarcinomas using reverse-transcription PCR (RT-PCR) and in situ hybridization, whereas mesothelin protein expression was evaluated by immunohistochemistry. RESULTS: Using an online SAGE database (http://www.ncbi.nlm.gov/SAGE), we found the tag for mesothelin to be consistently present in the mesothelioma, ovarian cancer, and pancreatic cancer libraries but not in normal pancreas libraries. Mesothelin mRNA expression was confirmed by in situ hybridization in 4 of 4 resected primary pancreatic adenocarcinomas and by RT-PCR in 18 of 20 pancreatic cancer cell lines, whereas mesothelin protein expression was confirmed by immunohistochemistry in all 60 resected primary pancreatic adenocarcinomas studied. The adjacent normal pancreas in these 60 cases did not label, or at most only rare benign pancreatic ducts showed weak labeling for mesothelin. CONCLUSIONS: Mesothelin is a new marker for pancreatic adenocarcinoma identified by gene expression analysis. Mesothelin overexpression in pancreatic adenocarcinoma has potential diagnostic, imaging, and therapeutic implications.

Arkossy, P., P. Toth, et al. (2002). "New reconstructive surgery of remnant pancreas in cases of

cancer of Vater's papilla." Hepatogastroenterology **49**(43): 255-7.

BACKGROUND/AIMS: The radical surgical procedure for treatment of the carcinoma of papilla of Vater is the pancreatoduodenectomy. The mortality rate of the surgery highly decreased in the last decade, nevertheless there are complications related to the complication of anastomosis of the remnant pancreas. METHODOLOGY: The authors introduce a new reconstructional procedure to decrease the complications. After the removal of the pancreatic head and body an end-to-side anastomosis was performed between the pancreatic duct and a Roux-en jejunal loop. The second anastomosis of the procedure was an end-to-side choledochojejunostomy, the third was an end-to-side duodenojejunostomy. The duodenojejunostomy is about 40 cm from the pancreatic anastomosis, keeping food far from the pancreas with the help of peristaltic waves. This method was applied in 6 patients. RESULTS: It was found that the new reconstructional procedure had generally favorable results without complication. CONCLUSIONS: This method of reconstruction allows for spontaneous closure and safe drainage of potential insufficient pancreaticojejunostomy. The recovered patients support future favorable usage of this new reconstructional surgical procedure.

Au, E. (2000). "Clinical update of gemcitabine in pancreas cancer." Gan To Kagaku Ryoho **27 Suppl 2**: 469-73.

Pancreatic cancer constitutes less than 2% of all cancers diagnosed in Singapore, consistent with the proportion described worldwide. About 40% of patients are diagnosed when the disease is locally advanced but without metastases. Another 40% are diagnosed with distant metastases. Only 20% are diagnosed when resectable. Most are adenocarcinomas arising from the head of the pancreas. Systemic chemotherapy is used for advanced metastatic pancreatic cancer but has met with limited success. Gemcitabine is a new fluorine-substituted cytarabine compound. In a randomised study it appears to confer statistically significant, although modest, improvement in quality of life and survival of patients with metastatic pancreas cancer. Evaluation of the drug in combination chemotherapy regimens and with radiation continues.

Avila, G. E., X. Zheng, et al. (2005). "Inhibitory effects of 12-O-tetradecanoylphorbol-13-acetate alone or in combination with all-trans retinoic acid on the growth of cultured human pancreas cancer cells and pancreas tumor xenografts in immunodeficient mice." J Pharmacol Exp Ther **315**(1): 170-87.

Treatment of cultured PANC-1, MIA PaCa-2, and BxPC-3 human pancreatic adenocarcinoma cells with 0.1 to 1.6 nM 12-O-tetradecanoylphorbol-13-acetate (TPA) for 96 h inhibited the proliferation of these cells in a dose-dependent manner, and PANC-1 and MIA PaCa-2 cells were more sensitive to TPA than BxPC-3 cells. Inhibition of proliferation by TPA in PANC-1 cells was associated with an increase in the level of p21, but this was not observed in MIA PaCa-2 or BxPC-3 cells. The TPA-induced increase of p21 in PANC-1 cells was blocked by bisindolylmaleimide or rottlerin (inhibitors of protein kinase C). Studies in NCr-immunodeficient mice with well established PANC-1 tumor xenografts indicated that daily i.p. injections of TPA strongly inhibited tumor growth, increased the percentage of caspase-3-positive cells, and decreased the ratio of mitotic cells to caspase-3-positive cells in the tumors. Studies with BxPC-3 tumors in NCr mice receiving daily i.p. injections of vehicle, TPA, all-trans retinoic acid (ATRA), or a TPA/ATRA combination showed that TPA had an inhibitory effect on tumor growth, but treatment of the animals with the TPA/ATRA combination had a greater inhibitory effect on tumor growth than TPA alone. Treatment with the TPA/ATRA combination resulted in a substantially decreased ratio of the percentage of mitotic cells to the percentage of caspase-3-positive cells in the tumors compared with tumors from the vehicle-treated control animals. The inhibitory effects of TPA on tumor growth occurred at clinically achievable blood levels.

Axilbund, J. E., K. A. Brune, et al. (2005). "Patient perspective on the value of genetic counselling for familial pancreas cancer." Hered Cancer Clin Pract **3**(3): 115-22.

PURPOSE: To assess patient views regarding the value of genetic counselling for familial pancreas cancer in the absence of predictive genetic testing. PATIENTS AND METHODS: At-risk adults with three or more relatives with pancreas cancer received genetic counselling prior to research screening via endoscopic ultrasound. Questionnaires were mailed after the visit to assess perceived value of the counselling session. RESULTS: Ninety-three percent of respondents felt genetic counselling for pancreas cancer was helpful despite the lack of a causative gene, while only 7% felt that it should not be offered until such a gene is discovered. Over half of respondents believed the pancreas cancer in their family was caused by a gene mutation, and 42% thought they had inherited the mutation. The average perceived lifetime risk of developing pancreas cancer was 51%, and 87% of respondents would ultimately seek predictive genetic testing. When more information is gained, 89% would be interested in

another genetic counselling session, and 82% would recommend current genetic counselling for pancreas cancer to a friend or relative with a family history of the disease. CONCLUSION: Despite the lack of an identified major causative gene for pancreas cancer, respondents found genetic counselling for this malignancy to be helpful. These patients perceive their personal cancer risk to be high, and would seek predictive genetic testing if it were available. Referral for genetic counselling should be offered to appropriate individuals.

Bachem, M. G., S. Zhou, et al. (2008). "Pancreatic stellate cells--role in pancreas cancer." Langenbecks Arch Surg **393**(6): 891-900.

BACKGROUND: Adenocarcinomas of the pancreas are characterized by a rapid progression, an early metastasis, a limited response to chemo- and radiotherapy, and an intense fibrotic reaction known as tumor desmoplasia. Carcinoma cells are surrounded by a dense stroma consisting of myofibroblast-like cells, collagens, and fibronectin. MATERIALS AND METHODS: This review describes the interaction of activated pancreatic stellate cells (myofibroblast-like cells) with tumor cells in pancreas adenocarcinomas. Our data were obtained in cell culture experiments and in in vivo investigations. RESULTS: Carcinoma cells produce soluble mediators and stimulate motility, proliferation, matrix-, and MMP synthesis of stellate cells. Vice versa-activated stellate cells release mitogens, stimulating proliferation of cancer cells. Cancer cell proliferation and resistance to apoptosis might further be induced by the microenvironment (extracellular matrix), which is primarily provided by stellate cells. A very important aspect in the interaction of stellate cells with cancer cells is the expression of EMMPRIN (extracellular matrix metalloproteinase inducer) by cancer cells, the shedding of the extracellular part of EMMPRIN by matrix metalloproteinases (MMPs), and the induction of MMPs in stellate cells by soluble EMMPRIN. In particular, the stellate cells in close proximity to tumor cells therefore express MMPs and degrade connective tissue. CONCLUSION: Through complex interactions between stellate cells and carcinoma cells, tumor progression and cancer cell invasion are accelerated. As we gain better understanding of these mechanisms, adequate therapies to reduce tumor cell invasion and cancer progression might be developed.

Banba, Y., T. Kanazawa, et al. (1998). "CT evaluation of gastric cancer: depth of tumor invasion and pancreas invasion." Radiat Med **16**(3): 161-6.

PURPOSE: To compare the internal structure of tumor and the contiguous organ configuration on computed tomography (CT) with the depth of tumor invasion on the pathological specimen. METHODS: Sixty-four gastric cancers depicted on incremental dynamic CT were classified according to the internal structure of the tumor, and correlated with the depth of tumor invasion. In addition, the cancers were classified according to the contiguous pancreatic configuration, and correlated with the degree of pancreatic invasion. RESULTS: Eleven tumors with thickened gastric wall consisting of both a thick inner layer of high attenuation and a thin outer layer of low attenuation (two-layered tumor with a thin outer layer) did not invade the serosa: mucosa (n = 5) and submucosa (n = 6). Of 59 gastric cancers with a regular margin to the contiguous pancreas, pancreatic invasion was absent in 58 and present in one. Pancreatic invasion was present in all of five gastric cancers with an irregular margin. CONCLUSIONS: Our results indicate that two-layered gastric tumors with a thin outer layer never invade the serosa. Furthermore, pancreatic invasion is predicted only when the margin of the contiguous pancreas is irregular.

Banville, N., R. Geraghty, et al. (2006). "Medullary carcinoma of the pancreas in a man with hereditary nonpolyposis colorectal cancer due to a mutation of the MSH2 mismatch repair gene." Hum Pathol **37**(11): 1498-502.

Pancreatic adenocarcinoma has been reported in kindreds with hereditary nonpolyposis colorectal cancer (HNPCC). Medullary carcinoma of the pancreas is a recently described rare variant of pancreatic adenocarcinoma. We describe a man with colorectal carcinoma who subsequently developed pancreatic medullary carcinoma. The tumor displayed microsatellite instability and loss of expression of the mismatch repair proteins MSH2 and MSH6. Mutational analysis of the mismatch repair genes MLH1 and MSH2 demonstrated a pathogenic nonsense mutation within the MSH2 gene, which is consistent with a diagnosis of HNPCC. This report adds support to an association between HNPCC and pancreatic adenocarcinoma displaying the medullary phenotype, suggesting that medullary features in a pancreatic carcinoma may point toward a genetic cancer predisposition. To our knowledge, this is the first reported case of medullary carcinoma of the pancreas in a patient with HNPCC due to a mutation of the MSH2 gene.

Bardeesy, N., K. H. Cheng, et al. (2006). "Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer." Genes Dev **20**(22): 3130-46.

SMAD4 is inactivated in the majority of pancreatic ductal adenocarcinomas (PDAC) with

concurrent mutational inactivation of the INK4A/ARF tumor suppressor locus and activation of the KRAS oncogene. Here, using genetically engineered mice, we determined the impact of SMAD4 deficiency on the development of the pancreas and on the initiation and/or progression of PDAC-alone or in combination with PDAC--relevant mutations. Selective SMAD4 deletion in the pancreatic epithelium had no discernable impact on pancreatic development or physiology. However, when combined with the activated KRAS(G12D) allele, SMAD4 deficiency enabled rapid progression of KRAS(G12D)-initiated neoplasms. While KRAS(G12D) alone elicited premalignant pancreatic intraepithelial neoplasia (PanIN) that progressed slowly to carcinoma, the combination of KRAS(G12D) and SMAD4 deficiency resulted in the rapid development of tumors resembling intraductal papillary mucinous neoplasia (IPMN), a precursor to PDAC in humans. SMAD4 deficiency also accelerated PDAC development of KRAS(G12D) INK4A/ARF heterozygous mice and altered the tumor phenotype; while tumors with intact SMAD4 frequently exhibited epithelial-to-mesenchymal transition (EMT), PDAC null for SMAD4 retained a differentiated histopathology with increased expression of epithelial markers. SMAD4 status in PDAC cell lines was associated with differential responses to transforming growth factor-beta (TGF-beta) in vitro with a subset of SMAD4 wild-type lines showing prominent TGF-beta-induced proliferation and migration. These results provide genetic confirmation that SMAD4 is a PDAC tumor suppressor, functioning to block the progression of KRAS(G12D)-initiated neoplasms, whereas in a subset of advanced tumors, intact SMAD4 facilitates EMT and TGF-beta-dependent growth.

Blackstock, A. W., J. E. Tepper, et al. (2003). "Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas." Int J Gastrointest Cancer **34**(2-3): 107-16.

PURPOSE: Determine the safety and efficacy of twice weekly gemcitabine and concurrent radiation to the upper abdomen followed by weekly gemcitabine in patients with surgically staged, locally advanced pancreatic cancer. METHODS: Patients with surgically staged, locally advanced, nonmetastatic adenocarcinoma of the pancreas were treated with intravenous gemcitabine administered twice weekly (40 mg/m2/d) for 5 wk concurrent with upper abdominal radiation (50.4 Gy in 180 cGy daily fractions over 5.5 wk). At the completion of the chemoradiation, patients without disease progression were given gemcitabine (1000 mg/m2) weekly for five cycles. Each cycle consisted of 3 wk of treatment followed by 1 wk without treatment. Disease progression and response were assessed at 6- to 8-wk intervals. RESULTS: From February through December 1999, 43 patients were entered into this phase II trial, 39 of whom were evaluable for treatment response. The median age was 59 yr (range: 39-84 yr); there were 18 males (47%) in the study. Grade III and IV hematologic toxicity occurred in 48 and 21% of patients, respectively, and was primarily leukocytopenia and neutropenia. Grade III and IV gastrointestinal toxicities occurred in 31 and 10% of patients, respectively. There was one death attributed to sepsis. The concurrent gemcitabine and radiation portion of the study was completed without treatment interruptions in 56% of patients. The overall median survival was 8.2 mo and the median survival in the 44% of patients demonstrating a sustained CA-19-9 response was 13.5 mo. Only six patients experienced local regional progression as their first site of failure. Two patients (5%) were still alive at 35 and 41 mo posttreatment. CONCLUSIONS: These results confirm the feasibility of twice weekly gemcitabine and radiation for the treatment of pancreatic cancer. Although this treatment strategy produced good local regional control, this did not result in a survival advantage. Stratifying patients by performance status and CA-19-9 response in future trials may be of value.

Boadas, J., J. Balart, et al. (2000). "Survival of cancer of the pancreas. Bases for new strategies in diagnosis and therapy." Rev Esp Enferm Dig **92**(5): 316-25.

OBJECTIVE: The ominous prognosis of pancreatic carcinoma (PC) has led to a nihilistic attitude among physicians, and to the need to develop better tools for diagnosis, staging and treatment. The aim of this study was to analyze a series of patients with PC in order to determine stage-related survival, and to try to improve diagnostic and therapeutic strategies. METHODS: This was a retrospective study of 167 patients diagnosed from 1987 to 1993. The diagnosis was based on cytological pathology findings or on a clinical course compatible with PC. TNM stage and survival were calculated. We also analyzed age, sex, time elapsed until diagnosis, diagnostic tests, size and location, cytologic pathology confirmation, number of patients undergoing surgery, and procedures used. RESULTS: Age: 67 +/- 12 years, 82 men and 85 women. Time elapsed until diagnosis: 3 +/- 15.7 months. Pathologic diagnosis: 74.8%. Location: head 75%, body 13.9%, tail 7.2%, diffuse 2.4%, not reported 1.2%. Size: 4.6 +/- 2 cm. TNM staging: stage I 13%; stage II 25%; stage III 20%; stage IV 42%. Stage-related survival: stage I 14 months; stage II 6 months; stage III 4 months; stage IV 1 month. Total survival: 3 months. Surgery was done in 66.5% and resection in 10%; curative surgery

in 6.5%; bypass in 81% and diagnostic laparotomy in 9%. In 55% of the patients surgery revealed a higher stage of disease than had been diagnosed preoperatively. Postoperative mortality was 18%. Survival at 1 and 5 years after curative surgery was 80% and 20%, respectively. CONCLUSIONS: Diagnosis was made at a late stage in many patients. Few patients were candidates for radical surgery. Early diagnosis, preoperative staging and postoperative management should be improved in these patients, and surgery should be associated with complementary chemotherapy and/or radiotherapy.

Bocci, G., R. Danesi, et al. (2004). "Antiangiogenic versus cytotoxic therapeutic approaches to human pancreas cancer: an experimental study with a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor and gemcitabine." Eur J Pharmacol **498**(1-3): 9-18.

Pancreatic adenocarcinoma is a leading cause of cancer death in the United States and represents a challenging chemotherapeutic problem. The pharmacological control of angiogenesis might represent a novel approach to the management of pancreas cancer, since the pathological development of vascular supply is a critical step for tumor growth and may affect its prognosis. In order to test this hypothesis, SU5416 ([3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one]) a selective inhibitor of the vascular endothelial growth factor receptor-2 tyrosine kinase, and gemcitabine (2', 2'-difluorodeoxycytidine) were tested on endothelial (HUVEC) and pancreatic tumor cells (MIA PaCa-2) in vitro and in vivo alone and in simultaneous association. SU5416 inhibited HUVEC cells stimulated to proliferate by vascular endothelial growth factor but not MIA PaCa-2 cells; the drug concentration that decreased cell growth by 50% (IC50) was 0.14 microM. Furthermore, SU5416 reduced the development of microvessels from placental explants (IC50, 0.23 microM). Gemcitabine inhibited the growth of both HUVEC and MIA PaCa-2 cells with an IC50 of 0.08 and 0.1 microM, respectively. A synergistic effect (combination index <1 and dose reduction index >1) on anti-proliferative and pro-apoptotic activity was calculated with the simultaneous combination of the two drugs on endothelial cells. A marked in vivo antitumor effect on MIA PaCa-2 xenografts was observed with SU5416 at a protracted schedules, as well as with gemcitabine; furthermore, the combination between the two drugs resulted in an almost complete suppression of tumor growth and relapse. In conclusion, the present results provide the evidence of an effective anti-endothelial/antitumor activity of protracted administration of SU5416 on human pancreas cancer xenografts, which is comparable with the one obtained by gemcitabine; moreover, the synergistic combination between these drugs on endothelial cells and the promising association in pancreatic cancer xenografts could be used in future studies and translated into the clinical setting.

Bown, S. G., A. Z. Rogowska, et al. (2002). "Photodynamic therapy for cancer of the pancreas." Gut **50**(4): 549-57.

BACKGROUND: Few pancreatic cancers are suitable for surgery and few respond to chemoradiation. Photodynamic therapy produces local necrosis of tissue with light after prior administration of a photosensitising agent, and in experimental studies can be tolerated by the pancreas and surrounding normal tissue. AIMS: To undertake a phase I study of photodynamic therapy for cancer of the pancreas. PATIENTS: Sixteen patients with inoperable adenocarcinomas (2.5-6 cm in diameter) localised to the region of the head of the pancreas were studied. All presented with obstructive jaundice which was relieved by biliary stenting prior to further treatment. METHODS: Patients were photosensitised with 0.15 mg/kg meso-tetrahydroxyphenyl chlorin intravenously. Three days later, light was delivered to the cancer percutaneously using fibres positioned under computerised tomographic guidance. Three had subsequent chemotherapy. RESULTS: All patients had substantial tumour necrosis on scans after treatment. Fourteen of 16 left hospital within 10 days. Eleven had a Karnofsky performance status of 100 prior to treatment. In 10 it returned to 100 at one month. Two patients with tumour involving the gastroduodenal artery had significant gastrointestinal bleeds (controlled without surgery). Three patients developed duodenal obstruction during follow up that may have been related to treatment. There was no treatment related mortality. The median survival time after photodynamic therapy was 9.5 months (range 4-30). Seven of 16 patients (44%) were alive one year after photodynamic therapy. CONCLUSIONS: Photodynamic therapy can produce necrosis in pancreatic cancers with an acceptable morbidity although care is required for tumours invading the duodenal wall or involving the gastroduodenal artery. Further studies are indicated to assess its influence on the course of the disease, alone or in combination with chemoradiation.

Boyle, P., P. Maisonneuve, et al. (1996). "Cigarette smoking and pancreas cancer: a case control study of the search programme of the IARC." Int J Cancer **67**(1): 63-71.

A multi-centre case-control study of pancreas cancer, designed to be population-based, to use a

random sample of local populations as controls and to use a common protocol and core questionnaire, was conducted as the first study of the SEARCH programme of the International Agency for Research on Cancer. "Ever-smokers" were found to be at increased risk for pancreas cancer compared with "never-smokers" consistently in all strata of gender, response status and centre. Risk of pancreas cancer was found to increase with increasing lifetime consumption of cigarettes, the relative risk rising to 2.70 (95% C.I. 1.95 to 3.74) in the highest intake category. The overall trend in risk was highly significant and the association was found consistently in each stratum of gender, response status and centre. Fifteen years had to pass from quitting cigarette smoking until the risk fell to a level compatible with that in never-smokers among the heaviest group of smokers; among the 2 lowest tertiles this happened within 5 years. Further, reported smoking habits more than 15 years before diagnosis appeared to have no influence on pancreas-cancer risk, irrespective of amount smoked. The results are consistent with a causal role for cigarette smoking in the aetiology of pancreas cancer and illustrate that ceasing to smoke cigarettes can lead to reductions in the elevated risk of pancreas cancer produced by this habit.

Brune, K., T. Abe, et al. (2006). "Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer." Am J Surg Pathol **30**(9): 1067-76.

We screened 116 patients with a strong family history of pancreatic cancer using a combination of endoscopic ultrasound and computed tomography. Ten of these patients underwent surgical resection at our institution, providing an opportunity to define the morphology of pancreatic precursor lesions in patients with a strong family history of pancreatic cancer. Eight of the 10 pancreata were available and these were entirely submitted for histologic examination. The number of pancreatic intraepithelial neoplasia (PanIN) lesions and intraductal papillary mucinous neoplasms (IPMNs) were compared with age-matched controls. Parenchymal changes were defined. Selected precursor neoplasms from 6 pancreata were microdissected and analyzed for KRAS gene mutations. PanINs were significantly more common in the 8 cases (mean of 10.7% of the duct profiles, range 1.0% to 27.3%) than in the controls (mean 1.9%, range 0% to 9.2%, P<0.01). Different KRAS gene mutations were identified in separately microdissected precursor lesions in 2 of 6 cases. IPMNs were identified in 4 of the 8 cases, including 2 pancreata each having 2 distinct IPMNs. Both the IPMNs and the PanINs, even the low-grade PanIN-1 lesions, were associated with lobular parenchymal atrophy. Some individuals with a strong family history of pancreatic cancer develop multifocal, noninvasive epithelial precursor lesions of the pancreas. PanINs and IPMNs produce obstructive lobular atrophy, and this atrophy is likely the source of the chronic pancreatitis-like changes seen in these patients. The multifocal nature of familial pancreatic neoplasia suggests that surveillance of these patients is warranted after partial pancreatectomy.

Burcharth, F., J. Trillingsgaard, et al. (2003). "Resection of cancer of the body and tail of the pancreas." Hepatogastroenterology **50**(50): 563-6.

BACKGROUND/AIMS: To report our results of resection of cancer in the body and tail of the pancreas and review the literature. METHODOLOGY: Thirteen patients with a median age of 62 years with cancer of the body and/or tail of the pancreas. The diagnosis was made by ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography and angiography. Eleven patients had distal or subtotal pancreatectomy and two patients total pancreatectomy. The surgical procedure included extensive dissection of lymph nodes and the connective tissue in the peripancreatic region. Main outcome measures were postoperative morbidity and mortality, median and 5-year survival rates. RESULTS: Ten of the resections were considered to be curative. Postoperative complications occurred in seven patients and one patient died in the postoperative period. The median survival time of operative survivors was 392 days. Two patients survived five years, and one was alive ten years after surgery. Eight patients died of recurrence. CONCLUSIONS: Long-term survival may be achieved in a quarter of the resectable patients.

Burris, H. and A. M. Storniolo (1997). "Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil." Eur J Cancer **33 Suppl 1**: S18-22.

An early study with gemcitabine in pancreas cancer indicated greater relief of disease-related symptoms than expected from the objective tumour response rate. A novel design was created to assess changes in symptomatology prospectively in two studies. The design focuses on typical features seen in patients with advanced pancreas cancer (pain, impaired function, weight loss) and the endpoint is 'clinical benefit response'. Traditional endpoints of objective tumour response and survival were also included. In a randomised study, the clinical benefit response rate for gemcitabine was 24% compared with

5% for 5-fluorouracil (5-FU) (P = 0.0022). The median survival was 5.65 months for gemcitabine compared with 4.41 months for 5-FU (P = 0.0025). The corresponding objective response rates were 5.4% and 0%. Disease stabilised in 39% and 19% of gemcitabine and 5-FU patients, respectively. In a second study of 5-FU-refractory patients, 27.0% of patients were clinical benefit responders. The median survival in this second study was 3.8 months; the objective response rate was 11%, and 30% of patients had stable disease. These trials show that gemcitabine improves disease-related symptoms and survival in patients with pancreas cancer.

Burris, H. A., 3rd, M. J. Moore, et al. (1997). "Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial." J Clin Oncol **15**(6): 2403-13.

PURPOSE: Most patients with advanced pancreas cancer experience pain and must limit their daily activities because of tumor-related symptoms. To date, no treatment has had a significant impact on the disease. In early studies with gemcitabine, patients with pancreas cancer experienced an improvement in disease-related symptoms. Based on those findings, a definitive trial was performed to assess the effectiveness of gemcitabine in patients with newly diagnosed advanced pancreas cancer. PATIENTS AND METHODS: 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/m2 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/m2 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 (> or = 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. RESULTS: Clinical benefit response was experienced by 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients (P = .0022). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively (P = .0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. Treatment was well tolerated. CONCLUSION: This study demonstrates that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms in patients with advanced, symptomatic pancreas cancer. Gemcitabine also confers a modest survival advantage over treatment with 5-FU.

Calvo, F. A., R. Matute, et al. (2004). "Neoadjuvant chemoradiation with tegafur in cancer of the pancreas: initial analysis of clinical tolerance and outcome." Am J Clin Oncol **27**(4): 343-9.

The early institutional experience in the neoadjuvant treatment of potentially resectable pancreatic carcinoma using oral Tegafur as radioenhancing agent is analyzed. Fifteen patients (10 male and 5 female, mean age of 61 years) were treated over a 30-month period. Tegafur dose was 1,200 mg/d along the external radiotherapy period (45-55 consecutive days). Preoperative radiotherapy achieved a total dose of 45 to 50 Gy (1.8 Gy/d). Intraoperative electron boost (10-15 Gy) was delivered at the time of surgery. Hematologic tolerance showed a significant decrease of neutrophil and platelet counts from the outset to the end of the neoadjuvant period (p = 0.001 and p = 0.004, respectively). Five grade III vomiting episodes (33%) were also registered. In 9 patients (60%), surgical resection was performed after chemoradiation. Three complete pathologic responses (pT0 specimens) were identified; in seven cases, the resection achieved tumor-free surgical margins of the specimen. With a median follow-up of 21 months, median survival time was 17 months, with actuarial rates of 45% at 1 year and 24% at 3 years. Median survival for the resected patients was 23 months, and for the unresected patients median survival was 8 months (p = 0.02). The overall median survival in completely resected patients was 28 months, with a 71% survival rate at 1 and 3 years. It is concluded that the treatment scheme described is feasible and acceptably tolerated. The use of oral Tegafur seems to induce results similar to those of other therapeutic protocols using intravenous radioenhancing chemotherapy.

Campani, D., I. Esposito, et al. (2001). "Bcl-2 expression in pancreas development and pancreatic cancer progression." J Pathol **194**(4): 444-50.

Apoptosis is important for both tissue development and differentiation; its deregulation may contribute to tumourigenesis. In order to clarify the role of Bcl-2, an apoptosis-inhibiting protein, in pancreatic morphogenesis and tumour progression, its immunohistochemical expression was evaluated in 12 samples of fetal pancreas, in 10 samples of adult pancreas with ductal hyperplastic lesions, in 120 cases of primary pancreatic ductal adenocarcinoma, and in 43 synchronous metastatic lymph nodes. To evaluate the role of apoptosis in pancreatic cancer, p53 expression was also studied in tumour samples. Bcl-2

cytoplasmic acinar and ductal immunostaining was found in all fetal and adult tissue samples; ductal hyperplastic lesions were constantly negative. Thirty out of 120 (25%) tumours and 3 out of 43 (7%) lymph nodes expressed Bcl-2, whereas 67 out of 120 (56%) expressed nuclear p53. Well-differentiated tumours (G1) were more frequently Bcl-2-positive (p=0.002); furthermore, there was an inverse correlation between Bcl-2 and p53 expression in primary tumours (p=0.02). Neither Bcl-2 nor p53 influenced patients' prognosis, which was instead affected by N (p=0.02) and M (p<0.0001) status and stage of the disease (p=0.002). It is concluded that Bcl-2 regulates pancreatic morphogenesis and tissue homeostasis from early fetal to adult life and can be considered a phenotypic marker of normal exocrine pancreas. On the other hand, the lack of expression in preneoplastic lesions and the low positivity found in primary tumours and lymph node metastases suggest that Bcl-2 does not play a centralrole in pancreatic tumourigenesis and cancer progression.

Cartwright, T., D. A. Richards, et al. (2008). "Cancer of the pancreas: are we making progress? A review of studies in the US Oncology Research Network." Cancer Control **15**(4): 308-13.

BACKGROUND: Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. In 2008, approximately 37,680 people will be diagnosed with pancreatic cancer and 34,290 will die of this disease. METHODS: The authors reviewed the literature on treatment of pancreatic cancer with an emphasis on studies conducted in the US Oncology Research (USOR) Network. RESULTS: Although much research has been conducted to develop improved systemic therapies of pancreatic cancer, gemcitabine as a single agent remains the current standard of care. Combinations with other chemotherapeutic drugs or biological agents have resulted in limited improvement. CONCLUSIONS: Despite aggressive efforts to improve treatment for patients with pancreatic cancer, limited progress has been made. It is hoped that new studies being planned and conducted will improve outcomes for patients with this disease.

Casadei, R., L. Piccoli, et al. (2004). "Inflammatory pseudotumor of the pancreas resembling pancreatic cancer: clinical, diagnostic and therapeutic considerations." Chir Ital **56**(6): 849-58.

Pancreatic masses could be malignant or benign. Among these latter inflammatory pseudotumor is an uncommon mass rarely located in the pancreas and it must be considered in differential diagnosis with pancreatic cancer. A case report and literature review of inflammatory pseudotumor were recognized to well known this rare pathology regarding its clinical, diagnostic, therapeutic and histopathological feature. Twenty-one cases of inflammatory pseudotumor in the adult were reviewed from the literature; 10 (47.6%) were female, 11 (52.3%) male; mean age 53.3 years (range 23-73). They were solid single mass in 18 cases, with median size of 5.1 cm (range 1.5-13), cystic mass in one case; 18 were located in the head, 1 in the body. In 2 cases it appeared as a volumetric increase of the pancreas. Diagnosis was possible only histologically and surgical treatment was mandatory in 20 cases; only in one patient a corticosteroid treatment was performed. Pancreatic inflammatory pseudotumor is a rare lesion of the pancreas but it must be distinguished from pancreatic cancer. Pancreatic resectioning is mainly due to the preoperative diagnostic difficulties that must be resolved surely only with histopathological examination of the specimen.

Chakrabarti, A., K. Zhang, et al. (2007). "Radiohybridization PET imaging of KRAS G12D mRNA expression in human pancreas cancer xenografts with [(64)Cu]DO3A-peptide nucleic acid-peptide nanoparticles." Cancer Biol Ther **6**(6): 948-56.

There is a compelling need to image pancreas cancer at an early stage. Human pancreas cancer cells display elevated levels of KRAS protein due to high copy numbers of KRAS mRNA, and elevated levels of insulin-like growth factor 1 receptor (IGF1R) due to overexpression of IGF1R mRNA. Therefore we hypothesized that pancreas cancer could be detected in vivo with a single probe that targets both KRAS mRNA and IGF1R. Because positron emission tomography (PET) is a sensitive imaging technique, we designed a probe incorporating the positron-emitting nuclide (64)Cu. The KRAS-specific hybridization probe consisted of 1,4,7-tris(carboxymethylaza)cyclododecane-10-aza-acetyl (DO3A) on the N-terminus of a peptide nucleic acid (PNA) hybridization sequence (GCCATCAGCTCC) linked to a cyclized IGF1 peptide analog (d-Cys-Ser-Lys-Cys) on the C-terminus, for IGF1R-mediated endocytosis. A series of such KRAS radiohybridization probes with 0, 1, 2 or 3 mismatches to KRAS G12D mRNA, including exact matches to wild type KRAS mRNA and KRAS G12V mRNA, along with a double d(Ala) replacement IGF1 peptide control, were assembled by continuous solid phase synthesis. To test the hypothesis that KRAS-IGF1 dual probes could specifically image KRAS mRNA expression noninvasively in human IGF1R-overexpressing AsPC1 pancreas cancer xenografts in immunocompromised mice, [(64)Cu]PNA radiohybridization probes and controls were administered by tail vein. The [(64)Cu]KRAS-IGF1

radiohybridization probe yielded strong tumor contrast in PET images, 8.6 +/- 1.4-fold more intense in the center of human pancreas cancer xenografts than in the contralateral muscle at 4 h post-injection. Control experiments with single base KRASmismatches, an IGF1 peptide mismatch, and a breast cancer xenograft lacking KRAS activation yielded weak tumor contrast images. These experiments are consistent with our hypothesis for noninvasive PET imaging of KRAS oncogene expression in pancreas cancer xenografts. Imaging oncogene mRNAs with radiolabel-PNA-peptide nanoparticles might provide specific genetic characterization of preinvasive and invasive pancreas cancers for staging and choice of therapy.

Cortesini, R. (2007). "Pancreas cancer and the role of soluble immunoglobulin-like transcript 3 (ILT3)." Jop **8**(6): 697-703.

Attempts to ameliorate the poor prognosis of pancreatic cancer have been largely unsuccessful. Interventions to enhance patients' immune responses to malignancies have been also largely unsuccessful. We now describe an immune-escape mechanism mediated by the inhibitory receptor immunoglobulin-like transcript 3 (ILT3) which may be responsible for such failures. Using a humanized severe combined immunodeficiency (SCID) mouse model, we demonstrate that soluble and membrane ILT3 induce CD8+ T suppressor cells and prevent rejection of allogeneic tumor transplants. Furthermore, we found that patients with carcinoma of the pancreas produce the soluble ILT3 protein, which induces the differentiation of CD8+ T suppressor cells and impairs T cell responses in mixed lymphocyte culture. These responses are restored by anti-ILT3 mAb or by depletion of sILT3 from the serum. Immunohistochemical staining of biopsies from the tumors and metastatic lymph nodes suggest that CD68+ tumor associated macrophages represent the major source of soluble ILT3. Alternative splicing, resulting in the loss of the ILT3 transmembrane domain may contribute to the release of ILT3 in the circulation. These data suggest that ILT3 depletion or blockade is crucial to the success of immunobiotherapy, particularly in pancreatic cancer.

Cote, M. L., M. Schenk, et al. (2007). "Risk of other cancers in individuals with a family history of pancreas cancer." J Gastrointest Cancer **38**(2-4): 119-26.

BACKGROUND: Inherited predisposition to pancreas cancer accounts for approximately 10% of cases. Familial aggregation may be influenced by shared environmental factors and shared genes. We evaluate whether a family history of pancreas cancer is a risk factor for ten specified cancers in first-degree relatives: bladder, breast, colon, head and neck, lung, lymphoma, melanoma, ovary, pancreas, and prostate. METHODS: Risk factor data and cancer family history were obtained for 1,816 first-degree relatives of pancreas cancer case probands (n = 247) and 3,157 first-degree relatives of control probands (n = 420). Unconditional logistic regression models using generalized estimating equations were used to estimate odds ratios (ORs), and 95% confidence intervals of having a first-degree relative a specified cancer. RESULTS: A family history of pancreas cancer was associated with a doubled risk of lymphoma (OR = 2.83, 95% CI = 1.02-7.86) and ovarian cancer (OR = 2.25, 95% CI = 0.77-6.60) among relatives after adjustment. Relatives with a family history of early-onset pancreas cancer in a proband had a sevenfold increased risk of lymphoma (OR = 7.31, 95% CI = 1.45 to 36.7). Relatives who ever smoked and had a family history of pancreas cancer had a fivefold increased risk of ovarian cancer (OR = 4.89, 95% CI = 1.16-20.6). CONCLUSION: Family history assessment of cancer risk should include all cancers. Assessment of other known and suspected risk factors in relatives will improve risk evaluation. As screening and surveillance methods are developed, identifying those at highest risk is crucial for a successful screening program.

Crawford, H. C., C. R. Scoggins, et al. (2002). "Matrix metalloproteinase-7 is expressed by pancreatic cancer precursors and regulates acinar-to-ductal metaplasia in exocrine pancreas." J Clin Invest **109**(11): 1437-44.

In gastrointestinal epithelium, metaplastic conversion between predominant cell types is associated with an increased risk of neoplasia. However, the mechanisms regulating metaplastic transitions in adult epithelia are largely undefined. Here we show that matrix metalloproteinase-7 (MMP-7) is expressed not only in the majority of human pancreatic ductal adenocarcinoma specimens, but also in human pancreatic intraepithelial neoplasia and metaplastic duct lesions in human and mouse. In a mouse model of pancreatic acinar-to-ductal metaplasia, MMP-7 progressively accumulates during the metaplastic transition, resulting in a concomitant increase in solubilization of Fas ligand (FasL). Under identical conditions, mice either deficient in MMP-7 or carrying an inactive FasL gene are severely inhibited in development of progressive metaplasia and acinar cell apoptosis. Thus, MMP-7 and FasL influence the initiation and maintenance of metaplastic events in pancreatic epithelium, explaining the observed link between metaplasia and apoptosis in pancreas and other gastrointestinal tissues.

Cullen, J. J., F. A. Mitros, et al. (2003). "Expression of antioxidant enzymes in diseases of the human pancreas: another link between chronic pancreatitis and pancreatic cancer." Pancreas **26**(1): 23-7.

INTRODUCTION: Chronic pancreatitis is a significant risk factor for pancreatic cancer and is associated with the generation of reactive oxygen species. Cells contain a large number of antioxidants to prevent or repair the damage caused by reactive oxygen species. There are three major types of primary intracellular antioxidant enzymes in mammalian cells: superoxide dismutase (SOD), catalase, and peroxidase, of which glutathione peroxidase is the most prominent. AIM: To determine the level of antioxidant enzymes in human pancreas from normal, chronic pancreatitis, and pancreatic cancer specimens. METHODOLOGY: Immunohistochemical analysis for manganese SOD, copper/zinc SOD, catalase, and glutathione peroxidase expression using the avidin-biotin-peroxidase complex method was performed on pancreatic specimens previously fixed in formalin and embedded in paraffin. A quantitative digital imaging methodology was used to examine antioxidant staining in the pancreatic tissue. Cytoplasmic regions of ductal and acinar cells were identified and digitized. Mean gray-level pixel values were then obtained for each of these regions. RESULTS: Cytoplasmic values of manganese SOD, catalase, and glutathione peroxidase were decreased in pancreatic cells from chronic pancreatitis specimens when compared with normal pancreas. In pancreatic carcinoma specimens, mean cytoplasmic gray-level values of all antioxidant enzymes were decreased when compared with normal pancreas. CONCLUSION: There appears to be a gradual decrease in antioxidant enzyme expression in pancreatic cells from normal pancreas to chronic pancreatitis to pancreatic cancer.

Cylwik, B., H. F. Nowak, et al. (1998). "AgNORs in duct epithelial lesions in chronic pancreatitis and in pancreas cancer cells." Hepatogastroenterology **45**(22): 1130-4.

BACKGROUND/AIMS: Argyrophilic nucleolar organizer regions (AgNORs) reflect the proliferative activity of cells. Since the majority of pancreatic cancers are ductal carcinomas, the aim of the study was to determine the AgNORs expression of potential pre-neoplastic ductal epithelial lesions in advanced chronic pancreatitis compared with pancreatic cancer cells. METHODOLOGY: Histological preparations obtained from 24 patients with chronic pancreatitis and 16 patients with pancreatic cancer were used to estimate the number of AgNORs per nucleus. Four types of AgNORs were distinguished and histograms with cell percentage of each type were performed for all forms of epithelial anomalies. RESULTS: In simple hyperplasia, squamous and mucous metaplasia the number of AgNORs ranged from 1.92 to 2.23; type I was predominant. In papillary hyperplasia, dysplasia and in situ carcinoma the number ranged from 2.98 to 3.34, with a predominance of type II-IV. In invasive carcinoma the number was 4.29 and 74% of cells were of type II-IV. CONCLUSIONS: Both counts of AgNORs and the percentage of type II-IV cells showed a gradual increase from simple hyperplasia through papillary hyperplasia and dysplasia to invasive carcinoma which in this respect differs significantly from all forms of the epithelial anomalies examined.

Czito, B. G., T. J. Hong, et al. (2006). "A phase I study of eniluracil/5-FU in combination with radiation therapy for potentially resectable and/or unresectable cancer of the pancreas and distal biliary tract." Cancer Invest **24**(1): 9-17.

PURPOSE: Eniluracil is an effective inactivator of dihydropyrimidine dehydrogenase (DPD). It allows for oral dosing of 5-fluorouracil (5-FU), which may potentially improve the antitumor activity of 5-FU when delivered concurrently with radiotherapy while avoiding the inconvenience and morbidity of continuous infusion (CI) 5-FU. We addressed the safety of oral eniluracil/5-FU combined with radiation therapy and determined the profile of dose-limiting toxicities and recommended Phase II dose (RPTD) in patients with pancreatic and hepatobiliary cancers. METHODS AND MATERIALS: Patients with resectable or locally advanced pancreatic and biliary cancer received eniluracil (starting at 6.0 mg/m(2) q12h)/5-FU (starting at 0.6 mg/m(2) q12h). Eniluracil/5-FU were given concurrently with preoperative radiation to 4500 cGy followed by 540 cGy by reduced fields. Surgery was considered 4 weeks after completion of therapy. RESULTS: Thirteen patients were enrolled. Chemoradiotherapy was completed in all patients. The MTD was not reached and, thus, the RPTD of eniluracil/5-FU was determined to be 10 mg/m(2) q12h/1 mg/m(2) q12h. Two patients with locally advanced disease had a 30-45 percent cross-sectional tumor reduction, one of which underwent margin-negative resection. Two of 5 patients with pancreatic cancer, and 1 of 3 patients with cholangiocarcinoma, with underwent exploratory surgery had margin-negative resections. One patient had a pathologic complete response (pCR). Patient 5-FU plasma exposure increased slightly from Day 8 to Day 31. CONCLUSION: Preoperative chemoradiation with oral eniluracil/5-FU is feasible, well tolerated, and potentially effective in the neoadjuvant setting.

Further investigation of oral fluoropyrimidines as radiosensitizers for pancreaticobiliary malignancies is warranted.

de Braud, F., S. Cascinu, et al. (2004). "Cancer of pancreas." Crit Rev Oncol Hematol **50**(2): 147-55.

Cancer of the pancreas is the tenth most frequent cancer in Europe, accounting for some 3% of cancer in both sex. Smoking has been clearly established as a major risk factor affecting the carcinogenesis of pancreatic carcinoma. Diet has also been associated with pancreatic cancer, although no conclusive data are yet available. Different genetic alterations have been observed in pancreatic neoplasms. Typical symptoms of pancreatic cancer are: jaundice, abdominal pain and weight loss. The prognosis of pancreatic carcinoma depends mainly on radical surgery and the presence of negative resection margins, as well as on the biological tumour stage, which also influences the treatment strategy. The treatment of pancreatic cancer is undertaken with two aims. Radical surgery is indicated for patients with early stage of disease, mainly stage I and partially II. In all other cases, the aim of treatment is the palliation of different very distressing symptoms related to this neoplasm.

Desai, S., E. Ben-Josef, et al. (2009). "Gemcitabine-based combination chemotherapy followed by radiation with capecitabine as adjuvant therapy for resected pancreas cancer." Int J Radiat Oncol Biol Phys **75**(5): 1450-5.

PURPOSE: To report outcomes for patients with resected pancreas cancer treated with an adjuvant regimen consisting of gemcitabine-based combination chemotherapy followed by capecitabine and radiation. PATIENTS AND METHODS: We performed a retrospective review of a series of patients treated at a single institution with a common postoperative adjuvant program. Between January 2002 and August 2006, 43 resected pancreas cancer patients were offered treatment consisting of 4, 21-day cycles of gemcitabine 1 g/m(2) intravenously over 30 min on Days 1 and 8, with either cisplatin 35 mg/m(2) intravenously on Days 1 and 8 or capecitabine 1500 mg/m(2) orally in divided doses on Days 1-14. After completion of combination chemotherapy, patients received a course of radiotherapy (54 Gy) with concurrent capecitabine (1330 mg/m(2) orally in divided doses) day 1 to treatment completion. RESULTS: Forty-one patients were treated. Median progression-free survival for the entire group was 21.7 months (95% confidence interval 13.9-34.5 months), and median overall survival was 45.9 months. In multivariate analysis a postoperative CA 19-9 level of >or=180 U/mL predicted relapse and death. Toxicity was mild, with only two hospitalizations during adjuvant therapy. CONCLUSIONS: A postoperative adjuvant program using combination chemotherapy with gemcitabine and either cisplatin or capecitabine followed by radiotherapy with capecitabine is tolerable and efficacious and should be considered for Phase III testing in this group of patients.

Dessimoz, J. and A. Grapin-Botton (2006). "Pancreas development and cancer: Wnt/beta-catenin at issue." Cell Cycle **5**(1): 7-10.

Beta-catenin and Adenomatous poliposis coli (APC) have been implicated in non-ductal pancreatic cancers. As for many other organs, several recent publications show that beta-catenin and more largely the Wnt pathway appear to function at the level of pancreatic progenitors and endocrine cells during organogenesis. This raises the question of the cell type in which beta-catenin is mutated during tumor formation in acinar cell carcinomas, pancreatoblastomas and solid cystic papillary tumors of the pancreas.

Distler, U., J. Souady, et al. (2009). "Shiga toxin receptor Gb3Cer/CD77: tumor-association and promising therapeutic target in pancreas and colon cancer." PLoS One **4**(8): e6813.

BACKGROUND: Despite progress in adjuvant chemotherapy in the recent decades, pancreatic and colon cancers remain common causes of death worldwide. Bacterial toxins, which specifically bind to cell surface-exposed glycosphingolipids, are a potential novel therapy. We determined the expression of globotriaosylceramide (Gb3Cer/CD77), the Shiga toxin receptor, in human pancreatic and colon adenocarcinomas. METHODOLOGY/PRINCIPAL FINDINGS: Tissue lipid extracts of matched pairs of cancerous and adjacent normal tissue from 21 pancreatic and 16 colon cancer patients were investigated with thin-layer chromatography overlay assay combined with a novel mass spectrometry approach. Gb3Cer/CD77 was localized by immunofluorescence microscopy of cryosections from malignant and corresponding healthy tissue samples. 62% of pancreatic and 81% of colon adenocarcinomas showed increased Gb3Cer/CD77 expression, whereas 38% and 19% of malignant pancreas and colon tissue, respectively, did not, indicating an association of this marker with neoplastic transformation. Also, Gb3Cer/CD77 was associated with poor differentiation (G>2) in pancreatic cancer (P = 0.039). Mass spectrometric analysis evidenced enhanced expression of Gb3Cer/CD77 with long (C24) and short chain fatty acids (C16) in malignant tissues and pointed to the presence of hydroxylated fatty acid lipoforms, which

are proposed to be important for receptor targeting. They could be detected in 86% of pancreatic and about 19% of colon adenocarcinomas. Immunohistology of tissue cryosections indicated tumor-association of these receptors. CONCLUSIONS/SIGNIFICANCE: Enhanced expression of Gb3Cer/CD77 in most pancreatic and colon adenocarcinomas prompts consideration of Shiga toxin, its B-subunit or B-subunit-derivatives as novel therapeutic strategies for the treatment of these challenging malignancies.

Doglietto, G. B., F. Pacelli, et al. (2000). "Pancreas-preserving total gastrectomy for gastric cancer." Arch Surg **135**(1): 89-94.

BACKGROUND: Pancreas-preserving total gastrectomy for gastric cancer has been proposed to remove lymph nodes along the upper border of the pancreas without performing a distal pancreatic resection. However, the original technique includes the ligation of the splenic artery at its origin and thus carries the risk of pancreatic necrosis. HYPOTHESIS: A technique of pancreas-preserving total gastrectomy that includes ligation of the splenic artery approximately 5 cm distally from the root may reduce the risk of postoperative pancreatic necrosis. DESIGN: Case series. SETTING: Both primary and referral hospital care. PATIENTS: Hospital records of 228 consecutive patients who, according to a personal technique, underwent D3 pancreas-preserving total gastrectomy for gastric cancer from 1981 to 1997 were reviewed. MAIN OUTCOME MEASURES: Surgical complications, postoperative deaths, and survival. RESULTS: Hospital morbidity and mortality were 33.3% and 3.9%, respectively. No patients experienced pancreatic necrosis. The 5-year survival rate after curative resection was 53.6%: 96.9% for stage IA, 76.3% for stage IB, 63.0% for stage II, 35.6% for stage IIIA, 27.0% for stage IIIB, and 20.3% for stage IV (N3-positive patients) disease. CONCLUSION: Results of the present study show the efficacy of this method of radical resection for gastric cancer as demonstrated by the low incidence of postoperative complications and high survival rates.

Eguchi, H., O. Ishikawa, et al. (2006). "Role of intraoperative cytology combined with histology in detecting continuous and skip type intraductal cancer existence for intraductal papillary mucinous carcinoma of the pancreas." Cancer **107**(11): 2567-75.

BACKGROUND: Intraductal papillary mucinous neoplasm (IPMN) is a recently discovered pancreatic tumor that has continuous or discontinuous (skip) lesions. Recent reports suggest a higher frequency of cancer recurrence in the remnant pancreas after surgical resection of IPMN. It is therefore important to precisely detect intraductal cancer extension and skip lesions when resecting IPMN. METHODS: Both intraoperative histologic examination of the surgical margin and cytologic examination of the pancreatic juice from each pancreatic segment (head, body, or tail) were performed on 43 IPMN patients. In addition to the preoperatively planned resection, 1 or 2 pancreatic segment(s) were additionally resected if the pancreatic juice tested positive in cytology. When a surgical margin was positive but the cytology in the remaining segment was negative, a subsegment (2-cm slice in width) was additionally resected until a negative margin was confirmed. RESULTS: Twenty-five patients (58%) demonstrated negative results in both histology and cytology obtained from the segment(s) that were not initially intended to be removed. In contrast to the preoperative estimation, 5 patients were found to have a positive surgical margin and negative cytology, 5 patients demonstrated a negative surgical margin and positive cytology, and 8 patients demonstrated a positive surgical margin and positive cytology. Investigations of the resected specimens revealed that 8 patients (19%) had skip lesions in addition to the main lesion. Logistic regression analysis revealed that patients with a dilated main pancreatic duct, or those with cancerous lesions in the main tumors, were at high risk for positive histology and/or cytology. CONCLUSIONS: Using intraoperative frozen-section histology and pancreatic juice cytology, 18 out of 43 patients in the current study (42%) required additional resection of the pancreas. A necessary and sufficient range of resection should be determined by intraoperative examination.

Elgamal, A. A., N. L. Ectors, et al. (1996). "Detection of prostate specific antigen in pancreas and salivary glands: a potential impact on prostate cancer overestimation." J Urol **156**(2 Pt 1): 464-8.

PURPOSE: We explored the immunohistochemical expression of prostate specific antigen (PSA) in pancreas and salivary glands. MATERIALS AND METHODS: We investigated 62 specimens from male and female subjects, representing normal cases and several pathological conditions of pancreas and salivary glands. Two commercially available monoclonal antisera for PSA and 1 for prostatic acid phosphatase were used. RESULTS: A consistently positive reaction for PSA and prostatic acid phosphatase, independent of patient sex, was noted in ductal cells of normal pancreas and normal salivary glands, as well as pleomorphic adenoma, adenocarcinoma and all oncocytic epithelial cells of Warthin's tumor. Reaction was absent in normal stromal and acinar cells, and squamous

carcinoma. CONCLUSIONS: PSA is detectable in normal and cancer tissues far from the prostate. Therefore, we may not entirely rely on specificity of PSA alone to diagnose metastatic prostate cancer.

El-Salhy, M., V. Tjomsland, et al. (2005). "Effects of triple treatment with octreotide, galanin and serotonin on a human pancreas cancer cell line in xenografts." Histol Histopathol **20**(3): 745-52.

Human pancreas cancer cells were implanted s.c. in nude mice. After 11 days, the mice were divided into two groups of 13. The first group received sterile saline solution and the second received triple therapy containing octreotide, galanin and serotonin, 40 microg/kg/day as a continuous i.p. infusion via an implanted osmotic pump for 14 days. Triple therapy prolonged the survival rate of the mice bearing human pancreatic carcinoma. Both the volume and weight of tumours in mice given triple therapy were less than in controls (not statistically significant). The proliferation index and the labelling index for epidermal growth factor (EGF) increased significantly in mice given triple therapy vis-a-vis controls. There was no statistically significant difference between control and treated tumours as regards, apoptotic index, necrosis, or number of tumour blood vessels. The increased survival rate was attributed to the reduced tumour load, since both weight and volume were reduced. It is most probable that octreotide was the responsible agent. Further investigation with single and double combinations of octreotide, galanin and serotonin are needed to identify the cause of increased cell proliferation in tumours subjected to these bioactive substances. Identifying the agent(s) inducing pancreatic cancer cell proliferation may be useful in combining a new treatment, as antagonists to these bioactive substances are available.

Fahrig, R., D. Quietzsch, et al. (2006). "RP101 improves the efficacy of chemotherapy in pancreas carcinoma cell lines and pancreatic cancer patients." Anticancer Drugs **17**(9): 1045-56.

RP101 [(E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)], which supports apoptosis and prevents the acquisition of chemoresistance, was tested in cultured human pancreatic tumor cells. RP101 downregulated uridine phosphorylase, a marker of poor prognosis, and APEX1, which is involved in DNA repair, and repressed Stat3 and its target vascular endothelial growth factor. Furthermore, RP101 activated antitumor immunity as demonstrated by enhanced cytolytic activity of NK-92 natural killer cells. This was concomitant with an enhanced expression of lymphotoxins alpha and beta, natural killer cell transcript 4, tumor necrosis factor LIGHT/TNFSF-14, and intercellular adhesion molecule-1 in pancreas carcinoma cells. These results encouraged us to investigate the effect of RP101 in pancreas cancer patients. Here, we present data from two RP101 combination therapy schemes. In a first pilot study, 13 patients in stage III and VI of the disease were treated with gemcitabine +cisplatin+RP101. RP101 co-treatment enhanced remissions, survival and time to progression. Seventy-seven percent of the patients lived or have lived longer than 1 year, and 23% have lived more than 2 years. Median survival was 447 days, time to progression 280 days and the response rate 33%. A second study with 21 patients in similar stages of disease, treated with RP101+gemcitabine alone, confirmed the results of the pilot study. Eighty-three percent of the presently evaluable patients live or lived 0.5 years or longer and 33% 1 year or longer. Considering both studies, the tumor control was 94%. The data indicate that acquisition of chemoresistance was prevented and the antitumor efficacy of standard chemotherapy was improved. To our knowledge, RP101 co-treatment is more efficient than any other regimen published.

Faigel, D. O., G. G. Ginsberg, et al. (1997). "Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions." J Clin Oncol **15**(4): 1439-43.

BACKGROUND: Endoscopic ultrasound (EUS) is an important new tool in the staging of pancreatic malignancies. Using new curved linear-array instruments, real-time fine-needle aspiration biopsy (RTFNA) of pancreatic lesions can be performed. METHODS: Forty-five patients with pancreatic lesions (22 males and 23 females) underwent staging with the Olympus EUM-20 (Olympus America Corp, Melville, NY) followed by EUS-RTFNA with the Pentax FG-32PUA (Pentax-Precision Instrument Corp, Orangeburg, NY) and the 22-gauge GIP needle (GIP Medizin Technik, Grassau, Germany). RESULTS: EUS tumor stages were as follows: TO, n = 1; T1, n = 8; T2, n = 9; and T3 n = 27. Aspiration attempts were unsuccessful in four patients (two technical failures and two inadequate specimens). The remaining 41 lesions (mean size, 3.3 cm) were aspirated under EUS guidance (median passes, three) and the cytologic diagnoses were 25 definite adenocarcinoma, five suspicious for adenocarcinoma (three subsequently confirmed and two clinical course consistent with adenocarcinoma), and 11 negative for malignancy. Of 11 negatives, two were found to have adenocarcinoma, seven were confirmed benign at surgery (four cystadenomas and three inflammatory), one had a benign pseudocyst, and one had abundant inflammatory cells on RTFNA and follow-up time greater than 12 months with computed tomographic (CT) scans consistent with

resolving inflammation. There were no false-positive RTFNAs. There were no procedure-related complications. Among those with diagnostic EUS-RTFNA (91%), the sensitivity for malignancy (confirmed plus suspicious) was 94% and negative predictive value 82%. CONCLUSION: EUS-guided RTFNA is a safe and accurate method for performing pancreatic biopsy. It should be considered in patients with suspected pancreatic malignancies in whom a tissue diagnosis is required or when other modalities have failed. EUS-RTFNA allows for local staging and tissue diagnosis in one procedure.

Farrell, J. J., M. van Rijnsoever, et al. (2005). "Early detection markers in Pancreas Cancer." Cancer Biomark **1**(2-3): 157-75.

The role of early detection in cancer has shown improved survival for certain cancers, including colon cancer, cervical cancer and breast cancer. The possibility for early detection of pancreatic cancer may be realized by an improved understanding of the histology and molecular genetics of precursor lesions and cancerous lesions in pancreatic cancer and the development of sensitive and specific screening tests (both invasive and non-invasive) to detect early pancreatic cancer. The NIH-NCI Early Detection Research Network (EDRN) in Pancreatic Cancer has been focussed on the development and validation of new biomarkers for the detection of early pancreatic cancer. This review will focus on our understanding of the histologic and molecular model of pancreatic carcinogenesis, current strategies and limitations of screening for pancreatic cancer and the development and validation of new biomarkers for the early detection of pancreatic cancer.

Fattahi, R., N. C. Balci, et al. (2009). "Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas." J Magn Reson Imaging **29**(2): 350-6.

PURPOSE: To compare diffusion-weighted imaging (DWI) findings and the apparent diffusion coefficient (ADC) values of pancreatic cancer (PC), mass-forming focal pancreatitis (FP), and the normal pancreas. MATERIALS AND METHODS: DWI (b = 0 and 600 seconds/mm(2)) findings of 14 patients with mass-forming FP proven by histopathology and or clinical follow-up, 10 patients with histopathologically-proven PC, and 14 subjects with normal pancreatic exocrine function and normal imaging findings were retrospectively evaluated. ADC values of the masses, the remaining pancreas, and the normal pancreas were measured. RESULTS: On b = 600 seconds/mm(2) DWI, mass-forming FP was visually indistinguishable from the remaining pancreas whereas PC was hyperintense relative to the remaining pancreas. The mean ADC value of PC (1.46 +/- 0.18 mm(2)/second) was significantly lower than the remaining pancreas (2.11 +/- 0.32 x 10(-3) mm(2)/second; $P < 0.0001$), mass-forming FP (2.09 +/- 0.18 x 10(-3) mm(2)/second; $P < 0.0001$), and pancreatic gland in the control group (1.78 +/- 0.07 x 10(-3) mm(2)/second; $P < 0.0005$). There was no significant difference of ADC values between the mass-forming focal pancreatitis and the remaining pancreas (2.03 +/- 0.2 x 10(-3) mm(2)/second; $P > 0.05$). CONCLUSION: Differences on DWI may help to differentiate PC, mass-forming FP, and normal pancreas from each other.

Fryzek, J. P., D. H. Garabrant, et al. (1997). "A case-control study of self-reported exposures to pesticides and pancreas cancer in southeastern Michigan." Int J Cancer **72**(1): 62-7.

A case-control study of pancreas cancer in residents, aged 30-79 years, of 18 counties in southeastern Michigan was conducted to investigate the risks of exposure to DDT and related materials in the general population. Sixty-six people with cytologically diagnosed pancreas cancer were identified using 7 participating hospitals in metropolitan Detroit and Ann Arbor. One hundred and thirty-one controls were frequency-matched to the cases on age, sex, ethicity and county of residence by random-digit dialing. All study participants were administered a questionnaire to assess life-time exposure to pesticides from both environmental and occupational sources, family history of cancer, past medical history, smoking history and demographic information. A statistically significant increased risk was found for self-reported exposure to ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane). Increased odds ratios were observed for self-reported exposures to chloropropylate and DDT, as well as for the summary group of organochlorine pesticides which included all of these materials, though these associations were not significant.

Garcia Picazo, D., P. Cascales Sanchez, et al. (2001). "Is pancreas and/or spleen resection required in total gastrectomy for advanced gastric cancer?" Rev Esp Enferm Dig **93**(7): 459-70.

OBJECTIVE: Total gastrectomy for advanced gastric cancer is frequently combined with extended lymphadenectomy. This technique is easier when resection of distal pancreas and/or spleen is performed. We have tried to evaluate whether the resection of both structures and total gastrectomy in patients with advanced gastric cancer actually improve survival rates. PATIENTS: From 1991 to 1999, 140

patients with advanced gastric cancer underwent total gastrectomy at the General Hospital of Albacete: 43 with simple total gastrectomy, 57 with total gastrectomy plus splenectomy and 40 with total gastrectomy plus distal pancreaticosplenectomy. Univariate and multivariate analysis were conducted in order to evaluate different prognostic factors and survival curves among the groups. RESULTS: Survival rates of the three groups were compared for each factor, being only significant variables the degree of tumor infiltration in the gastric wall, the size of the tumor, the staging and the type of lymphatic infiltration. Neither splenectomy nor distal pancreaticosplenectomy improved the survival compared to simple total gastrectomy. Morbimortality rates increased with more aggressive surgical procedures, but differences were not significant. CONCLUSIONS: Resection of distal pancreas and/or spleen plus total gastrectomy for advanced gastric cancer is associated to a greater number of isolated lymph nodes, but do not improve the survival of patients.

Ghadirian, P., G. Liu, et al. (2002). "Risk of pancreatic cancer among individuals with a family history of cancer of the pancreas." Int J Cancer **97**(6): 807-10.

In a hospital based case-control study of pancreatic cancer in Ontario and Quebec, a total of 174 incident pancreatic cancer cases and 136 healthy controls were compared for their family history of cancer. Information regarding the ages and sites of cancer was taken for 966 first-degree relatives of the cancer cases and for 903 first-degree relatives of the controls. A total of 150 cancer cases were reported among the relatives of the cases, compared to 122 cases among the relatives of the controls (relative risk 1.15; p = 0.23). Pancreatic cancer was the only site statistically in excess in the case relatives, compared to the control relatives (relative risk = 5.0; p = 0.01). The lifetime risk of pancreatic cancer was 4.7% for the first-degree relatives of the pancreatic cancer cases. The risk was 7.2% for relatives of cases diagnosed before age 60, and was 12.3% for relatives of patients with multiple primary cancers (all ages). These individuals comprise a high-risk group for pancreatic cancer and might benefit from enhanced surveillance or chemoprevention. Familial site-specific pancreatic cancer appears to be a distinct genetic entity, but contributes only modestly to the total burden of pancreatic cancer.

Giovannetti, E., M. Del Tacca, et al. (2006). "Transcription analysis of human equilibrative nucleoside transporter-1 predicts survival in pancreas cancer patients treated with gemcitabine." Cancer Res **66**(7): 3928-35.

Gene expression analysis may help the management of cancer patients, allowing the selection of subjects responding to treatment. The aim of this study was the characterization of expression pattern of genes involved in gemcitabine activity in pancreas tumor specimens and its correlation with treatment outcome. The role of drug transport and metabolism on gemcitabine cytotoxicity was examined with specific inhibitors, whereas transcription analysis of human equilibrative nucleoside transporter-1 (hENT1), deoxycytidine kinase (dCK), 5'-nucleotidase (5'-NT), cytidine deaminase (CDA), and ribonucleotide reductase subunits M1 and M2 (RRM1 and RRM2) was done by quantitative reverse transcription-PCR in tumor tissue isolated by laser microdissection from surgical or biopsy samples of 102 patients. Association between clinical outcome and gene expression levels was estimated using Kaplan-Meier method and Cox's proportional hazards model. Transport and metabolism had a key role on gemcitabine sensitivity in vitro; moreover, hENT1, dCK, 5'-NT, CDA, RRM1, and RRM2 were detectable in most tumor specimens. hENT1 expression was significantly correlated with clinical outcome. Patients with high levels of hENT1 had a significantly longer overall survival [median, 25.7; 95% confidence interval (95% CI), 17.6-33.7 months in the higher expression tertile versus median, 8.5; 95% CI, 7.0-9.9 months in the lower expression tertile]. Similar results were obtained with disease-free survival and time to disease progression, and the multivariate analysis confirmed the prognostic significance of hENT1. This study suggests that the expression levels of hENT1 may allow the stratification of patients based on their likelihood of survival, thus offering a potential new tool for treatment optimization.

Glimelius, B. (1998). "Chemotherapy in the treatment of cancer of the pancreas." J Hepatobiliary Pancreat Surg **5**(3): 235-41.

Opinions about the value of chemotherapy in pancreatic cancer vary from the idea that its use should be abandoned because of lack of proven efficacy and considerable toxicity to the idea that it may produce clinically meaningful responses correlated with improved survival. A systematic review of the available literature-based evidence was undertaken. The results are discussed in relation to supportive evidence from recent studies focusing on patient benefit. Six randomized trials of chemotherapy in advanced disease and two in the adjuvant setting with a no-active treatment group were identified. All eight trials were small, and the methodology was not always what is currently desirable. One of four palliative trials reported during the early 1980s, and

both trials completed during the 1990s showed a slight survival benefit with chemotherapy. In one of the trials, quality of life (QoL) was also more often improved after 5-fluorouracil-based chemotherapy than after best supportive care. Supportive evidence for a slight prolongation of survival and a clinical benefit also comes from trials comparing different drugs. No standard regimen is defined, although one drug, gemcitabine, has been approved in some countries for the treatment of advanced pancreatic cancer. The two randomized adjuvant trials included a very small number of patients, and, although a survival benefit was seen, conclusive evidence supporting the use of adjuvant chemo (radio) therapy is still lacking. Chemotherapy has low activity in advanced pancreatic cancer, but it can improve survival and well-being in some patients.

Griffin, C. A., L. Morsberger, et al. (2007). "Molecular cytogenetic characterization of pancreas cancer cell lines reveals high complexity chromosomal alterations." Cytogenet Genome Res **118**(2-4): 148-56.

Karyotype analysis can provide clues to significant genes involved in the genesis and growth of pancreas cancer. The genome of pancreas cancer is complex, and G-band analysis cannot resolve many of the karyotypic abnormalities seen. We studied the karyotypes of 15 recently established cell lines using molecular cytogenetic tools. Comparative genomic hybridization (CGH) analysis of all 15 lines identified genomic gains of 3q, 8q, 11q, 17q, and chromosome 20 in nine or more cell lines. CGH confirmed frequent loss of chromosome 18, 17p, 6q, and 8p. 14/15 cell lines demonstrated loss of chromosome 18q, either by loss of a copy of chromosome 18 (n = 5), all of 18q (n = 7) or portions of 18q (n = 2). Multicolor FISH (Spectral Karyotyping, or SKY) of 11 lines identified many complex structural chromosomal aberrations. 93 structurally abnormal chromosomes were evaluated, for which SKY added new information to 67. Several potentially site-specific recurrent rearrangements were observed. Chromosome region 18q11.2 was recurrently involved in nine cell lines, including formation of derivative chromosomes 18 from a t(18;22) (three cell lines), t(17;18) (two cell lines), and t(12;18), t(15;18), t(18;20), and ins(6;18) (one cell line each). To further define the breakpoints involved on chromosome 18, YACs from the 18q11.2 region, spanning approximately 8 Mb, were used to perform targeted FISH analyses of these lines. We found significant heterogeneity in the breakpoints despite their G-band similarity, including multiple independent regions of loss proximal to the already identified loss of DPC4 at 18q21.

Grimm, J., A. Potthast, et al. (2003). "Magnetic resonance imaging of the pancreas and pancreatic tumors in a mouse orthotopic model of human cancer." Int J Cancer **106**(5): 806-11.

Pancreatic adenocarcinoma has a rising incidence and a very poor survival rate. To develop new treatment strategies, extensive research is performed on animal models of pancreatic cancer. Orthotopic pancreatic tumors models, where the tumor is implanted into the pancreas, resemble the human disease more closely than subcutaneous tumor models, yet are difficult to monitor. In our study we report a magnetic resonance imaging (MRI) approach to visualize the pancreas in mice and to monitor orthotopically implanted pancreatic tumors. An MRI scanner was used to image normal murine pancreas and the pancreas of mice implanted with a human pancreatic adenocarcinoma cell line. Gadolinium (Gd)-DTPA-enhanced T1- and T2-weighted standard sequences were used with the objective to identify the pancreas and to monitor the growth of orthotopic tumors during 30 days. The pancreas as well as the implanted tumors could be easily identified using MRI. On T2-weighted images, the implanted tumors were easily visualized at the implantation side with high signal intensity. After application of a contrast agent, the tumors showed an enhancement. Heterogeneities within the tumor could be delineated, corresponding to histology, and the size of the tumor could be measured precisely. MR serves as a noninvasive high-resolution image modality to monitor murine pancreas as well as size, growth and even areas of heterogeneity in orthotopic pancreatic tumors.

Haller, D. G. (2003). "New perspectives in the management of pancreas cancer." Semin Oncol **30**(4 Suppl 11): 3-10.

Improvements in the management of locally advanced or metastatic pancreas cancer have proven to be both difficult and frequently marked by nihilism. Gemcitabine has replaced 5-fluorouracil-based chemotherapy as the standard of care. Gemcitabine first generated improvements in symptom control and survival in advanced disease, spurring further research. Subsequent trials have suggested that combinations of other agents with gemcitabine may extend clinical benefits to larger populations of patients. Newer combined chemoradiotherapy approaches may benefit the small population of patients with resectable disease, as well as the larger number of patients with locally advanced disease. In addition to identifying new cytotoxic agents and biologics, a greater challenge to clinical researchers is the development of innovative tools to diagnose and stage patients with pancreas cancer, and to monitor

and assess their response to therapy. This applies not only to individual patients but also to large-scale clinical trials.

Hanbidge, A. E. (2002). "Cancer of the pancreas: the best image for early detection--CT, MRI, PET or US?" Can J Gastroenterol **16**(2): 101-5.

Pancreatic cancer has a poor prognosis, and the best chance for survival is to diagnose the tumour at an early stage. Abdominal ultrasound, computed tomography, magnetic resonance imaging and endoscopic retrograde cholangiopancreatography are the most commonly used radiological techniques for imaging the pancreas. The diagnostic evaluation should be tailored to the individual patient. Dual-phase helical computed tomography and magnetic resonance imaging have similar accuracies for detecting and staging pancreatic adenocarcinoma. Sonography results are highly dependent on the skill and persistence of the operator. No radiological examination is very sensitive at visualizing small metastases in the lymph nodes and peritoneum, or on the surface of the liver. Thus, it is difficult to establish with certainty whether a tumour is resectable. Another major challenge is to differentiate cancer from an inflammatory mass in chronic pancreatitis. Functional imaging (using positron emission tomography with fluorodeoxyglucose) may be helpful, especially if the images are fused with those of computed tomography or magnetic resonance imaging. The diagnostic accuracies, applications and limitations of the various modalities are discussed.

Harnack, L. J., K. E. Anderson, et al. (1997). "Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study." Cancer Epidemiol Biomarkers Prev **6**(12): 1081-6.

To assess the relationship of smoking and coffee, tea, and alcohol intake to the risk of cancer of the exocrine pancreas, analyses were performed using data from a prospective cohort study of 33,976 postmenopausal Iowa women who responded to a mailed questionnaire in 1986 and were followed through 1994 for cancer incidence and total mortality. At baseline, information on cigarette smoking, consumption of tea, coffee, and alcoholic beverages, and other dietary and lifestyle factors was obtained. Age-adjusted relative risks of pancreatic cancer (n = 66 cases) showed a dose-response association with smoking. Those with fewer than 20 pack-years and those with 20 or more pack-years of smoking exposure were 1.14 (95% confidence interval, 0.53-2.45) and 1.92 (95% confidence interval, 1.12-2.30) times more likely, respectively, to develop pancreatic cancer than were nonsmokers. Current smokers were twice as likely as were nonsmokers to develop pancreatic cancer. Relative risks of pancreatic cancer increased with the amount of alcohol consumed (Ptrend = 0.11) after adjustment for age, smoking status, and pack-years of smoking. Relative risks of pancreatic cancer according to alcoholic beverage intake were as strong among never-smokers as they were in the total cohort. After the data were adjusted for age, smoking status, and pack-years of smoking, there was a statistically significant 2-fold (95% confidence interval, 1.08-4.30) elevated risk of pancreatic cancer for those who drank > 17.5 cups of coffee per week, compared to those who consumed < 7 cups/week; among never-smokers, the relative risks across coffee intake categories were still positive but were attenuated somewhat (P trend = 0.17). Tea intake was not related to cancer incidence. In summary, these findings provide evidence of an association of both alcoholic beverage and coffee consumption with pancreatic cancer incidence that is independent of age and cigarette smoking.

Heller, A. R., T. Rossel, et al. (2004). "Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients." Int J Cancer **111**(4): 611-6.

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 (FO) 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, we hypothesized that FO supplementation after major abdominal cancer surgery would improve hepatic and pancreatic function. Ours 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 (SO 1.0 g/kg body weight daily, n = 20) for 5 days or a combination of FO and SO (FO 0.2 + SO 0.8 g/kg body weight daily, n = 24). Compared to pure SO supplementation in the postoperative period, FO significantly reduced ASAT [0.8 +/- 0.1 vs. 0.5 +/- 0.1 mmol/(l. sec)], ALAT [0.9 +/- 0.1 vs. 0.6 +/- 0.1 mmol/(l. sec)], bilirubin (16.1 +/- 5.3 vs. 6.9 +/- 0.6 mmol/l), LDH (7.7 +/- 0.4 vs. 6.7 +/- 0.4 mmol/(l. sec) and lipase (0.6 +/- 0.1 vs. 0.4 +/- 0.1 micromol/(l. sec) 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 SO emulsion of 1.1 +/- 2.2 kg was absent in the FO group. After major abdominal tumor surgery, FO supplementation improved liver and pancreas function, which might have contributed to the faster recovery of patients.

Helm, J., B. A. Centeno, et al. (2009). "Histologic characteristics enhance predictive value of American Joint Committee on Cancer staging in resectable pancreas cancer." Cancer **115**(18): 4080-9.

BACKGROUND: American Joint Committee on Cancer (AJCC) anatomic stage group is considered relatively nondiscriminatory for predicting differences in survival after pancreatectomy for ductal adenocarcinoma, a perception confirmed in the authors' patients and by other reports. The authors' aim was to investigate the potential for improving the predictive value of AJCC staging by incorporating individually predictive histologic features into AJCC tumor-node-metastasis classification of anatomic extent, and determine the simplest combination of tumor characteristics predicting survival. METHODS: The authors determined survival of 137 patients who underwent pancreatectomy for ductal adenocarcinoma with curative intent (stage Groups IA-IIB) at Moffitt Cancer Center during the last 2 decades using data obtained from medical record review, the Moffitt Cancer Registry, and the Social Security Death Index. Histologic characteristics were confirmed by expert review. RESULTS: Median survival was 21.2 months after pancreatectomy with a 3-year disease-specific survival of 36%. Univariate Kaplan-Meier analysis and multivariate Cox proportional hazard modeling found worse survival with local extrapancreatic extension, poorly differentiated histology, and lymphatic invasion within tumor (P<.05). Survival was not worse with nodal metastases, microscopically positive resection margins, and perineural or venous invasion, nor was survival better with cancer arising from an intraductal papillary mucinous neoplasm. Kaplan-Meier estimates for different variable combinations showed prognosis was best for well- or moderately differentiated tumors without lymphatic invasion and confined to the pancreas (9.9 years median survival), worst for poorly differentiated tumors with lymphatic invasion and local extension beyond the pancreas (8.5 months median survival), and intermediate for well- or moderately differentiated tumors with either lymphatic invasion or local extension beyond the pancreas (21.2 months median survival). CONCLUSIONS: A simple combination of tumor differentiation, lymphatic invasion within the tumor, and local extrapancreatic extension predicts survival after pancreatectomy for ductal adenocarcinoma.

Herbella, F. A., A. C. Tineli, et al. (2008). "Gastrectomy and lymphadenectomy for gastric cancer: is the pancreas safe?" J Gastrointest Surg **12**(11): 1912-4.

INTRODUCTION: Resection of the capsule of the pancreas is part of the radical operation proposed by oriental authors for the treatment of gastric cancer. It is unclear; however, if resection of the capsule is a safe procedure or even if it is necessary. This study aims to assess in patients treated for gastric cancer the occurrence of: (a) pancreatic fistula and (b) metastasis to the pancreatic capsule. METHODS: We studied 80 patients (mean age 61 years, 42 males) submitted to gastrectomy with resection of the pancreatic capsule by hydrodissection. Patients with pancreatic disease, tumoral invasion of the pancreas, submitted to concomitant splenectomy, or anastomotic leakage were excluded. The tumor was located in the distal third of the stomach in 60% of the patients, in the middle third in 27%, and proximally in 12%. Total gastrectomy was performed in 27% of the cases and partial gastrectomy in 73%. In all patients, amylase activity in the drainage fluid was measured on day 2. If initial measurement was abnormal, subsequent measurements were performed in alternated days until normalization. Pancreatic fistula was defined as amylase levels greater than 600. In 25 of these patients (mean age 53 years, 16 males), the pancreatic capsule was histologically analyzed for metastasis. RESULTS: Pancreatic fistula was diagnosed in eight (10%) patients. The mean amylase level was 5,863. Normalization of amylase levels was achieved within 7 days in all patients. No patient developed clinical signs of fistula besides abnormal amylase levels in the drainage fluid, such as intra-abdominal abscesses. Pancreatic fistula was associated to younger age ($p = 0.03$) but not to gender ($p = 0.1$), tumor location ($p = 0.6$), and type of gastrectomy ($p = 0.8$). Metastasis to the pancreatic capsule was not identified. CONCLUSION: In conclusion, resection of the pancreatic capsule must be discouraged due to subclinical pancreatic fistula in a significant number of the cases and absence of metastasis.

Herlin, G., B. Persson, et al. (2003). "11C-harmine as a potential PET tracer for ductal pancreas cancer: in vitro studies." Eur Radiol **13**(4): 729-33.

Our objective was to find a tracer in diagnosing human pancreatic cancer using positron emission tomography (PET). For this purpose in vitro test of pancreatic tissues with autoradiography was used. Autoradiography was performed with (11)C-harmine (a MAO-A-inhibitor) with and without

competitive inhibition. Tissue preparations were obtained from normal human pancreas and pancreatic cancer. The uptake was compared with rat brain or pig brain, tissues with high expression of MAO-A. Nine autoradiography studies on 16 samples from five different human pancreatic cancers gave a significant level of specific binding of (11)C-harmine in 13, and 3 samples did not give a significant level of specific binding of (11)C-harmine. All 16 samples were analysed with autoradiography. Compared with rat brain, the uptake in the human cancers varied between 9 and 43% except for one tissue preparation which had a too low value for measurement. This study shows expression of MAO-A in human pancreatic cancer. This is readily characterised in vitro. The potential use of (11)C-harmine in the diagnosis of pancreatic cancer using PET might be limited, but further PET studies are necessary.

Herve, J., A. S. Cunha, et al. (2008). "Internal radiotherapy of liver cancer with rat hepatocarcinoma-intestine-pancreas gene as a liver tumor-specific promoter." Hum Gene Ther **19**(9): 915-26.

The hepatocarcinoma-intestine-pancreas (HIP) gene, also called pancreatitis-associated protein-1 (PAP1) or Reg IIIalpha, is activated in most human hepatocellular carcinomas (HCCs) but not in normal liver, which suggests that HIP regulatory sequence could be used as efficient liver tumor-specific promoters to express a therapeutic polynucleotide in liver cancer. The sodium iodide symporter (NIS), which has recognized therapeutic and reporter gene properties, is appropriate to evaluate the transcriptional strength and specificity of the HIP promoter in HCC. For this purpose, we constructed a recombinant rat HIP-NIS adenoviral vector (AdrHIP-NIS), and evaluated its performance as a mediator of selective radioiodide uptake in tumor hepatocytes. Western blot, immunofluorescence, and iodide uptake assays were performed in AdrHIP-NIS-infected primary hepatocytes and transformed hepatic and nonhepatic cells. Nuclear imaging, tissue counting and immunohistochemistry were performed in normal and HCC-bearing Wistar rats infected with AdrHIP-NIS intratumorally or via the hepatic artery. In AdrHIP-NIS-infected transformed hepatic cells, functional NIS was strongly expressed, as in cells infected with a cytomegalovirus-NIS vector. No NIS expression was found in AdrHIP-NIS-infected normal hepatocytes or transformed nonhepatic cells. In rats bearing multinodular HCC, AdrHIP-NIS triggered functional NIS expression that was preferential in tumor hepatocytes. Administration of 18 mCi of (131)I resulted in the destruction of AdrHIP-NIS-injected nodules. This study has identified the rHIP regulatory sequence as a potent liver tumor-specific promoter for the transfer of therapeutic genes, and AdrHIP-NIS-mediated (131)I therapy as a valuable option for the treatment of multinodular HCC.

Hirano, S., E. Tanaka, et al. (2007). "Feasibility of en-bloc wedge resection of the pancreas and/or the duodenum as an alternative to pancreatoduodenectomy for advanced gallbladder cancer." J Hepatobiliary Pancreat Surg **14**(2): 149-54.

Pancreatoduodenectomy has been described as a possible treatment for gallbladder cancer that presents with evidence of direct invasion to the pancreas and/or the duodenum. This procedure does, however, carry a significantly higher morbidity and mortality if performed with a hepatectomy. An alternative procedure, therefore, of wedge resection of the invaded organ(s) was investigated in this study. On recognition of infiltration of the tumor into the pancreas and/or the duodenum, an en-bloc wedge resection of the organ(s) combined with the original tumor was the intended procedure. However, a pancreatoduodenectomy was performed if the tumor was not resectable by an attempted wedge resection. Operative and long-term outcomes were compared between patients who underwent wedge resection (n = 9) and pancreatoduodenectomy (n = 8). One patient in each group was incorrectly diagnosed preoperatively as having cancer invasion, as opposed to inflammatory changes, as recognized by subsequent histology. All tumors were excised with tumor-free pancreatic and duodenal margins. Postoperative complications occurred in one patient with wedge resection and four with pancreatoduodenectomy. One in-hospital death occurred in each group; one patient died with wedge resection of sepsis and one patient with pancreatoduodenectomy died of a pancreatic leak. No local recurrence occurred in either group. There was no difference in cumulative survival rates between the groups. Wedge resection was considered to be a feasible surgical procedure, in terms of morbidity, respectability, and long-term outcome.

Huang, W. Y., L. Yue, et al. (2009). "Prognostic value of CRM1 in pancreas cancer." Clin Invest Med **32**(6): E315.

PURPOSE: Pancreatic cancer is a highly aggressive malignant tumour with poor prognosis. The median survival is only 6 months. This study investigated the prognostic value of nuclear export protein chromosomal region maintenance/exportin 1/Xpo1 (CRM1) expression in pancreas cancer. METHODS: CRM1 expression was detected, by Western blot, in pancreatic tissue from 69 cancer patients and 10 normal subjects. RESULTS: CRM1 showed increased expression in pancreatic cancer tissue (P = 0.007). The high expression of CRM1 was

associated with increased serum levels of CEA (P = 0.002) and CA19-9 (P = 0.005). There was an association between CRM1 expression and tumour size (P = 0.01), lymphadenopathy (P = 0.004) and liver metastasis (P = 0.003). High CRM1 expression was not correlated with the other clinicopathological parameters. High CRM1 expression was a prognostic indicator for progression-free survival (PFS) (P = 0.006) as well as overall survival (OS) (P = 0.001). Expression of CRM1 was an independent prognostic parameter for poorer PFS and OS (95% CI, 1.27-5.39). CONCLUSIONS: CRM1 expression demonstrated prognostic value in pancreatic cancer. Prospective studies are required to determine the prognostic role of high expression of CRM1 in pancreatic cancer.

Huguier, M., H. Baumel, et al. (1996). "Cancer of the exocrine pancreas. A plea for resection." Hepatogastroenterology **43**(9): 721-9.

BACKGROUND/AIMS: The aim of this retrospective multicentric study was to compare the results of resections with those of surgical palliative procedures. MATERIAL AND METHODS: The 3231 patients included had histologically proven adenocarcinoma of the pancreas and were operated on between 1982 and 1988. Seven hundred eighty-seven underwent surgical resection, and 2444 a palliative procedure. Step by step logistic regression was used to determine variables having the greatest impact on post operative mortality. Survivals were compared with the logRank test. A semi parametric Cox model was applied to estimate adjusted relative risk of death. RESULTS: After resection and bypass, postoperative mortality was 10% and 15% (P < 0.001), morbidity 35% and 27% (P < 0.001), and mean survival times 19.5 months (SE = 1.1), and 8.8 months (SE = 0.3) (P < 0.001) respectively. In patients without metastases, survival was better after resection than after bypass, even in patients with involvement of lymph nodes adjacent to or distant from the tumor (P = 0.001). CONCLUSIONS: In spite of the retrospective nature of such comparisons, these results acredit the idea that in patients with pancreatic cancer without metastases, resection should be attempted whenever possible.

Huguier, M. and N. P. Mason (1999). "Treatment of cancer of the exocrine pancreas." Am J Surg **177**(3): 257-65.

BACKGROUND: The incidence of cancer of the exocrine pancreas varies among populations, being the fourth or fifth cause of cancer death in the West. Outcome remains poor and opinions remain divided over the optimal management of the condition. METHOD: A computer literature search was made of the MEDLINE database from January 1990 to December 1997 and selected other studies. RESULTS: Indications and contraindications for surgery, indications for stenting, indications for resection, the technique of palliative procedures and of resection, chemotherapy, radiotherapy, and combined treatments and other treatments are discussed and recommendations made. CONCLUSIONS: Irrespective of tumor size or spread, resection if feasible gives the best survival rates. Careful patient selection is required, however, to exclude those patients for whom surgical resection has no benefit. Nonsurgical procedures including endoscopic stenting in patients with high operative risk or short survival expectancy can significantly improve quality of life. The place of adjuvant therapies remains controversial and further controlled trials are required to demonstrate their efficacy.

Hur, H., H. M. Jeon, et al. (2008). "Laparoscopic pancreas- and spleen-preserving D2 lymph node dissection in advanced (cT2) upper-third gastric cancer." J Surg Oncol **97**(2): 169-72.

BACKGROUND AND OBJECTIVES: Although the laparoscopic assisted total gastrectomy (LATG) has been performed in upper gastric cancer, dissection of lymph nodes No. 10 and 11d without resection of the distal pancreas and the spleen has been hard to accomplish, because of the possibilities of injury to splenic vessels and parenchyma of the spleen or pancreas. Herein, we present successful results in laparoscopic pancreas- and spleen-preserving D2 lymph node dissection in advanced upper gastric cancer. METHODS: Between March 2004 and May 2007, 18 clinical T2 patients who underwent LATG with D2 lymph node dissection for upper gastric cancer were enrolled. RESULTS: We used the technique of encircling and pulling the splenic artery with umbilical tape and that helped us complete dissection of lymph nodes No. 10 and 11d without distal pancreatectomy or splenectomy. The mean operative time was 370 min without any perioperative complications or conversion to an open procedure. CONCLUSIONS: Laparoscopic extended lymph node dissection without pancreatectomy or splenectomy can be adapted to the patients with clinical T2 upper gastric cancer. The techniques like taping of the splenic artery can be a useful tip for surgeons who wish to perform laparoscopic complete D2 lymph node dissection in advanced upper gastric cancer.

Hurtado, M., J. J. Lozano, et al. (2007). "Activation of the epidermal growth factor signalling pathway by tissue plasminogen activator in pancreas cancer cells." Gut **56**(9): 1266-74.

BACKGROUND: Tissue plasminogen activator (tPA) is the major activator of plasminogen in plasma. This serine protease is overexpressed by exocrine pancreas tumour cells, where it promotes tumour cell proliferation, growth, and invasion. Here we have explored the signalling pathways used by tPA to activate the proliferation of pancreatic cancer cells. METHODS: Transcriptional profiling on cDNA micro arrays was used to analyse the pattern of gene expression in response to tPA compared to the response to epidermal growth factor (EGF) and platelet derived growth factor (PDGF). Results were confirmed using different biochemical assays in which specific kinase inhibitors or RNA interference were used. RESULTS: Transcriptional profiling showed that tPA modulates the expression of a set of genes commonly regulated by EGF, but distinct from the major set of genes modulated by PDGF. This suggested that tPA and EGF share common signalling pathways, a conclusion supported by further experimental evidence. Firstly, we found that tPA induced a rapid and transient phosphorylation of the EGFR. Secondly, specific EGFR kinase inhibitors, but not PDGFR kinase inhibitors, abolished the tPA induced phosphorylation of the ERK1/2 kinases and cell proliferation. The mitogenic activity of tPA was also inhibited by siRNA depletion of EGFR, thus confirming the involvement of this receptor in tPA triggered signalling. Thirdly, we show that the signalling and mitogenic effects of tPA require its proteolytic activity, the activity of the metalloprotease-9 and active hb-EGF. CONCLUSION: Our results suggest that tPA induces proliferation by triggering a proteolytic cascade that sequentially activates plasmin, metalloprotease-9 (MMP-9) and hb-EGF. These events are required to activate the EGFR signalling pathway and cell proliferation.

Hustinx, S. R., R. H. Hruban, et al. (2005). "Homozygous deletion of the MTAP gene in invasive adenocarcinoma of the pancreas and in periampullary cancer: a potential new target for therapy." Cancer Biol Ther **4**(1): 83-6.

Methylthioadenosine phosphorylase (MTAP) plays an important role in the salvage pathway for the synthesis of adenosine. Novel chemotherapeutic strategies exploiting the selective loss of MTAP function in cancers have been proposed. The MTAP gene, on chromosome 9p21, is frequently included within homozygous deletions of the p16INK4A/CDKN2A gene. Biallelic deletions of the p16INK4A/CDKN2A gene are found in 40% of pancreatic cancers, suggesting that the MTAP gene may be frequently inactivated in pancreatic cancer and that selected patients with pancreatic cancer may benefit from therapies targeting this loss. We immunolabeled six xenografted pancreatic cancers with known MTAP and p16INK4A/CDKN2A gene status and found that immunolabeling mirrored gene status. Loss of expression of both MTAP and p16 was observed only in those pancreatic cancers with homozygous deletions that encompassed both the MTAP and p16INK4A/CDKN2A genes. We then immunolabeled a series of 320 microarrayed infiltrating pancreatic adenocarcinomas, 35 biliary adenocarcinomas, 54 ampullary cancers, and 35 noninvasive intraductal papillary mucinous neoplasms. Immunolabeling for MTAP was lost in 91 of the 300 (30%) evaluable pancreatic cancers, 9 of 54 (17%) ampullary cancers, 4 of 33 (12%) biliary cancers, and in 1 of 35 (3%) IPMNs. All neoplasms with loss of MTAP labeling also demonstrated loss of p16 labeling. These results suggest that MTAP expression is lost in approximately 30% of infiltrating pancreatic cancers and in a lower percentage of other periampullary neoplasms, that this loss is the result of homozygous deletions encompassing both the MTAP and p16INK4A/CDKN2A genes. Thus, pancreatic cancer is a promising cancer type in which to explore novel chemotherapeutic strategies to exploit the selective loss of MTAP function.

Iso, Y., N. Tagaya, et al. (2008). "Xanthogranulomatous lesion of the pancreas mimicking pancreatic cancer." Med Sci Monit **14**(11): CS130-3.

BACKGROUND: Xanthogranulomatous lesion is a rare condition that can develop in the gall bladder, kidney, and retroperitoneal space. This lesion is an inflammatory disease. It is commonly accepted that Xanthogranulomatous lesion of the pancreas (XGP) is hardly distinguishable from pancreatic neoplasms. As a result of the similarity of pancreatic cancer in clinical and imaging diagnostic findings, most of all patients have often been performed excessive surgeries. CASE REPORT: An 82-year-old male was admitted to our hospital because of body weight loss. Laboratory tests showed the presence of inflammation, and a Positron emission tomography (PET) revealed positive uptake in the pancreas head and tail, and spleen. Duodeno scopy showed excretion of mucin from the papilla of Vater. Intraductal ultrasonography (IOUS) showed a tumor located at the pancreas tail. Under a preoperative diagnosis of intraductal papillary mucinous carcinoma (IPMC) at the pancreas tail with metastasis to the spleen, distal pancreatectomy and splenectomy were performed. Microscopic findings of the operative specimen revealed massive infiltration of macrophages with fibrosis, the lost of ductal epithelium, and the severe deposition of amyloid and mucin with thrombosis.

Pathological diagnosis was XGP. The patient was uneventfully discharged from hospital on the postoperative day 22. Although XGP is a benign condition, most cases are treated by surgery same as our case. This is due to the difficulty in differenciating the lesion from pancreatic cancer. CONCLUSIONS: We reported a rare case of XGP mimicking pancreatic cancer. XGP should be added to one of differential diagnosis of pancreatic cancer.

Jacobs, N. L., F. G. Que, et al. (2009). "Cumulative morbidity and late mortality in long-term survivors of exocrine pancreas cancer." J Gastrointest Cancer **40**(1-2): 46-50.

BACKGROUND: Less than 5% of patients diagnosed with exocrine pancreas cancer live to be long-term survivors (5+ years after diagnosis). As a result, few studies have focused on these patients' cumulative, cancer-related morbidity and late mortality. This descriptive study was undertaken to explore such issues. METHODS: One thousand eight hundred thirty consecutive patients who had exocrine pancreas cancer had been seen at the Mayo Clinic between 1995 and 2001 and who had well-documented evidence of having lived for 5+ years were the focus of this study. RESULTS: Only 85 patients (4.6%) met all the above criteria. These patients had a median age of 65 years with a slight female predominance (53%). Eighty-one (95%) were treated with surgery, 42 (49%) with chemotherapy, and 41 (48%) with radiation. Cumulative morbidity included one or more subsequent surgeries in 17 patients (20%), one or more major infections in 14 (16%), diabetes in 39 (45%), depression in 16 (19%), and a second malignancy in 17 (20%). Twenty-nine patients were deceased at the time of this report; 15 (18%) died from recurrent pancreas cancer more than 5 years after their original diagnosis. CONCLUSION: Long-term survivors of exocrine pancreas cancer confront notable rates of cumulative morbidity, which include subsequent major surgeries, major infections, diabetes, depression, and second malignancies, as well as late deaths from pancreas cancer itself.

Kemp, C. (1999). "Metastatic spread and common symptoms. Part six: Advanced cancer of the pancreas, prostate, stomach, and uterus." Am J Hosp Palliat Care **16**(5): 673-81.

This is the last article in a six-part series on metastatic spread and natural history of the 18 most lethal tumors. The articles summarize symptom/problem anticipation, cancer metastasis, and the 18 tumors that each cause more than 6000 deaths/year in the United States. Bladder and brain cancer were discussed, with information given on tumor types, metastatic spread and invasion, and common symptoms. Parts II, III, IV, and V charted the natural histories, problems, and assessment parameters of advanced cancers of the breast, colon and rectum, esophagus, kidney, liver, and lung; and leukemia, melanoma, multiple myeloma, non-Hodgkin's lymphoma, and cancers of the oral cavity (and pharynx) and ovary. Part VI finishes the series with discussions of cancers of the pancreas, prostate, stomach, and uterus. Each of these cancers is presented separately, with information given on mortality rates, the most common tumor types, sites of metastases, common problems, and common oncology emergencies. Sites of spread, resulting problems (including site-specific symptoms), and assessment parameters are presented as tables. Material is presented so that clinicians are able to anticipate the spread of these cancers and can thus identify problems early in their development so that the problems are more easily managed.

Kimmelman, A. C., A. F. Hezel, et al. (2008). "Genomic alterations link Rho family of GTPases to the highly invasive phenotype of pancreas cancer." Proc Natl Acad Sci U S A **105**(49): 19372-7.

Pancreas ductal adenocarcinoma (PDAC) is a highly lethal cancer that typically presents as advanced, unresectable disease. This invasive tendency, coupled with intrinsic resistance to standard therapies and genome instability, are major contributors to poor long-term survival. The genetic elements governing the invasive propensity of PDAC have not been well elucidated. Here, in the course of validating resident genes in highly recurrent and focal amplifications in PDAC, we have identified Rio Kinase 3 (RIOK3) as an amplified gene that alters cytoskeletal architecture as well as promotes pancreatic ductal cell migration and invasion. We determined that RIOK3 promotes its invasive activities through activation of the small G protein, Rac. This genomic and functional link to Rac signaling prompted a genome wide survey of other components of the Rho family network, revealing p21 Activated Kinase 4 (PAK4) as another amplified gene in PDAC tumors and cell lines. Like RIOK3, PAK4 promotes pancreas ductal cell motility and invasion. Together, the genomic and functional profiles establish the Rho family GTP-binding proteins as integral to the hallmark invasive nature of this lethal disease.

Kitagami, H., S. Kondo, et al. (2007). "Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from Pancreatic Cancer Registry of Japan Pancreas Society." Pancreas **35**(1): 42-6.

OBJECTIVES: Acinar cell carcinoma (ACC) of the pancreas is a rare tumor, and many aspects

remain unclear because no large-scale clinical studies have been conducted. METHODS: The present study investigated the clinical characteristics, treatment, and therapeutic outcomes of 115 patients registered in the Pancreatic Cancer Registry of the Japan Pancreas Society, and therapeutic plans were reviewed. RESULTS: Although ACC has been associated with advanced stage and poor prognosis, this tumor was resectable in 76.5% of the patients, and the 5-year survival rate after resection was favorable, being 43.9%. CONCLUSIONS: Confirming the diagnosis of ACC preoperatively is difficult, but this diagnosis should be kept in mind while planning surgery for ordinary pancreatic cancer. Once the diagnosis has been confirmed, a possibility of surgical resection should be pursued to achieve better prognosis. If ACC is unresectable or recurrent, chemotherapy is likely to prove useful. Multidisciplinary therapy centering on the role of surgery will need to be established.

Kitamura, N., S. Murata, et al. (2003). "Obstructive jaundice in a metastatic tumor of the pancreas from breast cancer: a case report." Jpn J Clin Oncol **33**(2): 93-7.

Metastatic pancreas tumors from breast cancer are comparatively uncommon and patients with this tumor usually remain asymptomatic during their life. A 55-year-old woman presented with obstructive jaundice following mastectomy for invasive ductal carcinoma. We diagnosed obstructive jaundice due to a pancreatic tumor demonstrated on computed tomography and performed percutaneous transhepatic cholangio-drainage. Although the patient recovered from the jaundice, she had exacerbation of pneumonia from which she died. At autopsy, invasive ductal carcinoma was found in the pancreas tumor. Immunohistochemical staining was performed to confirm whether the pancreatic tumor was primary or secondary. Human milk fat globules 1 and 2 and gross cystic disease fluid protein-15, which characteristically exist in normal breast tissue or breast carcinoma, were expressed both in the primary breast tumor and the pancreatic tumor. In contrast, both the anti-estrogen receptor and anti-progesterone receptor antibodies stained positively in the primary breast cancer; however, neither of them was positive in the metastatic pancreatic tumor. We report a rare case of a patient who presented with obstructive jaundice from a pancreatic tumor metastasizing from breast cancer and in whom immunohistochemical staining using the antibodies unique to the mammary gland was effective for the diagnosis of this secondary tumor.

Klinkenbijl, J. H., J. Jeekel, et al. (1999). "Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group." Ann Surg **230**(6): 776-82; discussion 782-4.

OBJECTIVE: The survival benefit of adjuvant radiotherapy and 5-fluorouracil versus observation alone after surgery was investigated in patients with pancreatic head and periampullary cancers. SUMMARY BACKGROUND DATA: 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. METHODS: Eligible patients with T1-2N0-1aM0 pancreatic head or T1-3N0-1aM0 periampullary cancer and histologically proven adenocarcinoma were randomized after resection. RESULTS: 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 19.0 months for the observation group and 24.5 months in the treatment group (log-rank, $p = 0.208$). The 2-year survival estimates were 41% and 51 %, respectively. The results when stratifying for tumor location showed a 2-year survival rate of 26% in the observation group and 34% in the treatment group (log-rank, $p = 0.099$) in pancreatic head cancer; in periampullary cancer, the 2-year survival rate was 63% in the observation group and 67% in the treatment group (log-rank, $p = 0.737$). No reduction of locoregional recurrence rates was apparent in the groups. CONCLUSIONS: Adjuvant radiotherapy in combination with 5-fluorouracil is safe and well tolerated. However, the benefit in this study was small; routine use of adjuvant chemoradiotherapy is not warranted as standard treatment in cancer of the head of the pancreas or periampullary region.

Kobayashi, S., H. Shirasawa, et al. (1999). "P16INK4a expression adenovirus vector to suppress pancreas cancer cell proliferation." Clin Cancer Res **5**(12): 4182-5.

The prognoses of pancreatic cancer patients have been miserable even after radical surgery, and adjuvant therapy is necessary to improve the surgical results. p16(INK4a) (p16) is tight-binding and inhibitory protein for cyclin-dependent kinase 4 to

induce G1 arrest of the cell cycle. p16 gene deletion is frequently identified in human pancreas cancer. The impaired gene function of p16 might be a major factor of the uncontrolled proliferation and malignancy of pancreas cancer cells. In this study, we investigated the effect of adenovirus p16 expression vector for pancreas cancer cell proliferation to clarify whether the vector might be a promising mode to assist the surgical therapy for pancreas cancer. We constructed the adenovirus p16 expression vector AdexCACSp16 by inserting p16 cDNA to a cassette cosmid containing a nearly full-length adenovirus type 5 genome with E1 and E3 deletions. Thereafter, we assessed the activity of AdexCACSp16 to induce p16 gene mRNA expression in pancreas cancer cell line MIAPaCa-2 and to control cell proliferation. AdexCACSp16 induced a high level of p16 gene mRNA expression in MIAPaCa-2 cells with 1 h contact to the cells. The cell proliferation was significantly suppressed by AdexCACSp16 compared with the control adenovirus group. These data indicate that AdexCACSp16 has the potential to induce p16 gene expression and control pancreas cancer cell proliferation and that the adenovirus p16 expression vector AdexCACSp16 might be a possible method of gene therapy to improve the surgical therapeutic results for pancreas cancer.

Kondo, S., H. Katoh, et al. (2000). "Preoperative embolization of the common hepatic artery in preparation for radical pancreatectomy for pancreas body cancer." Hepatogastroenterology **47**(35): 1447-9.

BACKGROUND/AIMS: To assess preliminary results of preoperative embolization of the common hepatic artery in preparation for distal pancreatectomy with en bloc resection of the celiac and common hepatic arteries for carcinoma of the body of the pancreas involving these arteries. METHODOLOGY: Four patients underwent the embolization with coils 1-7 (median: 5) days before surgery. A detachable coil was used to obtain the best position of the first coil as an anchor in 3 patients. RESULTS: Immediately after embolization, collateral pathways developed from the superior mesenteric artery via the pancreatoduodenal arcades to the proper hepatic and gastroduodenal arteries in all 4 patients; however, they were relatively poor in one patient. There were no complications after embolization. The pulsation of the proper hepatic and gastroduodenal arteries was well palpable during surgery, although it had been compromised sometimes in previous cases without embolization. There were no ischemia-related complications in the 2 patients who underwent radical surgery. CONCLUSIONS: Preoperative embolization of the common hepatic artery is a safe technique and has the potential to enlarge the collateral pathways by the time of distal pancreatectomy with en bloc resection of the celiac artery and prevent postoperative fatal ischemia-related complications.

Konno, H., M. Baba, et al. (1997). "Measurement of pancreatic blood flow to prevent pancreatic juice leakage after pancreas-preserving total gastrectomy for gastric cancer." Eur Surg Res **29**(4): 287-91.

In patients with gastric cancer, distal pancreatectomy was frequently performed for complete removal of the lymph nodes along the splenic artery, but this procedure sometimes induced pancreatic juice leakage, subphrenic abscess, and postoperative diabetes. To avoid these complications, pancreas-preserving total gastrectomy (PP) was developed by Maruyama et al. [World J Surg 1995; 19:552-536], with which the spleen, splenic artery, and fatty connective tissue including lymph nodes could be removed completely without distal pancreatectomy. From 1988 to 1995, 36 patients underwent PP in our department. Although there were no operative deaths and no patient developed postoperative diabetes, pancreatic juice leakage was observed in 4 patients (11.1%). We assumed that ischemia of the distal pancreas may have caused this pancreatic juice leakage and investigated the relationship between pancreatic blood flow (PBF) and this complication in 12 recent patients. A significant negative correlation between PBF in the pancreatic tail and the peak amylase level (PAL) in the drain fluid was demonstrated. Two patients with PBF values of 4.5 and 5.2 ml/min/100 g tissue, respectively, and a PAL of more than 2 x 10(5) U/l developed pancreatic juice leakage, whereas the 10 patients without this complication had PBF values above 6 ml/min/100 g tissue and a PAL of less than 2 x 10(4) U/l. These results suggest that measurement of PBF may be useful to predict the leakage of pancreatic juice after PP and that distal pancreatectomy may be preferable when PBF is extremely low.

Kubota, E., H. Kataoka, et al. (2009). "Advanced stomach and pancreas cancer successfully treated with combination chemotherapy with S-1/paclitaxel/lentinan." Hepatogastroenterology **56**(89): 106-10.

We report a case of stomach and pancreas cancers that showed marked responses to combination chemotherapy consisting of S-1, paclitaxel (PTX), and lentinan (LNT). A 67-year-old Japanese man was referred to our hospital in July 2005, diagnosed with advanced gastric cancer. Subsequent examination revealed the existence of cancers in the stomach and pancreas, with lymph nodes and peritoneal metastasis and ascites. The patient received combined chemotherapy (one course comprised 3 weeks) with

S-1 (100 mg/body, day 1-14 followed by withdrawal for 1 week), PTX (50 mg/m2, day 1 and day 8), and LNT (2 mg/m2, day 1, day 8 and day 15). After completion of 4 courses, the patient achieved partial response (PR), with complete disappearance of the primary gastric tumor and ascites. He maintained in PR for 17 months. We analyzed Th1/ Th2 ratio and LNT binding rate to monocytes by flow cytometry. Combination chemotherapy with S-1/PTX/LNT can be an effective treatment for unresectable advanced gastric carcinoma.

Kullenberg, B., C. Jansen, et al. (2000). "Transforming growth factor alpha (TGF-alpha) increases cell number in a human pancreatic cancer cell line but not in normal mouse pancreas." Int J Pancreatol **28**(3): 199-205.

BACKGROUND: The pancreas harbors growth factors such as the epidermal growth factor (EGF) family. The physiological and pathophysiological roles of growth factors in normal pancreas remain unsettled. Human pancreatic cancer overexpresses the EGF receptor, and the ligands EGF and transforming growth factor alpha (TGF-alpha). The aim of the present experiments was to study the effect of TGF-alpha in a pancreatic cancer cell line and in normal mouse pancreas. METHOD: The LN-36 cell line, established from a pancreatic duct cell adenocarcinoma, was incubated with TGF-alpha or EGF. The effect of an EGF receptor-specific, tyrosine kinase inhibitor (tyrphostin B56) with or without growth factors was also studied. The cell number was measured with the XTT-colorimetric method. TGF-alpha, the tyrphostins A25, B48, and B56, were in separate experiments infused during 1 wk to normal female mice by subcutaneous (sc) minipumps. RESULTS: The LN-36 cell line responded to TGF-alpha and EGF with increased cell number; +61% with 10(-10) M TGF-alpha and +34% with 10(-9) M EGF. Tyrphostin B56 at a concentration of 10(-5) M reduced the cell number by 76%, but when incubated together with growth factors the reduction was only 44% with TGF-alpha, and 39% with EGF. Infusion of TGF-alpha increased mouse pancreatic wet weight and protein content but was without effect on DNA synthesis, measured as incorporation of tritiated thymidine. Infusion of three different tyrphostins did not influence mice pancreas. CONCLUSION: The results support the role of TGF-alpha to maintain growth of pancreatic cancer cells by the EGF receptor. Infusion of TGF-alpha induced hypertrophy in normal mouse pancreas.

Kurosaki, I., K. Hatakeyama, et al. (2008). "Portal vein resection in surgery for cancer of biliary tract and pancreas: special reference to the relationship between the surgical outcome and site of primary tumor." J Gastrointest Surg **12**(5): 907-18.

BACKGROUND: Early and late outcomes after superior mesenteric-portal vein resection (VR) combined with pancreaticoduodenectomy, major hepatectomy, or both for pancreaticobiliary carcinoma were retrospectively evaluated. VR is the most frequently used vascular procedure in this field, but an exact role of VR has not been compared according to the primary site of tumor. MATERIALS AND METHODS: Postoperative outcomes were compared between surgery with and without VR in each of the three disease-based groups: hilar cholangiocarcinoma and intrahepatic cholangiocarcinoma with hilar extension (HIC, 56), middle and distal cholangiocarcinoma and gallbladder carcinoma (DGC, 118), and pancreatic head adenocarcinoma (PHC, 77). RESULTS: VR was performed in 19.6% of HIC, 8.5% of DGC, and 45.5% of PHC. In-hospital death was 7.1% (4 of 56) patients with VR (3 of DGC and 1 of PHC). Operations with VR in DGC showed a larger amount of blood loss and more increased ratio of R1operation than those with no VR. In HIC, DGC, and PHC, median survival time of patients with VR was 37, 6.8, and 20 months and that of patients without VR was 42.9, 28.6, and 20.3 months, respectively. VR did not affect survival either in HIC or in PHC; however, in DGC, VR was accompanied with dismal outcome compared with no VR (p=0.001). CONCLUSIONS: Aggressive surgery with VR can be justified both in HIC and in PHC but should not be recommended for DGC. Surgical outcomes of VR differed considerably, depending on the sites of the primary tumor.

Lapointe, R., R. Letourneau, et al. (2005). "Phase II study of troxacitabine in chemotherapy-naive patients with advanced cancer of the pancreas: gastrointestinal tumors." Ann Oncol **16**(2): 289-93.

BACKGROUND: Troxacitabine (Troxatyl) is a novel L-enantiomer nucleoside analog with activity in pancreatic cancer xenograft models. PATIENTS AND METHODS: Troxacitabine 1.5 mg/m(2) was administered by 30-min infusions daily x5 every 4 weeks to 54 patients with advanced pancreatic cancer. Patients were evaluated for objective tumor response, time to tumor progression (TTP), changes in tumor marker CA 19-9, survival, safety, pain, analgesic consumption, Karnofsky performance status and weight change. RESULTS: Median TTP was 3.5 months (95% CI 2.0-3.8), median survival 5.6 months (95% CI 4.9-7.4), and the 1 year survival rate 19%. Best responses were stable disease in 24 patients with eight patients having stable disease for at least 6 months (15%). A 50% or greater decrease in CA 19-9 was seen in seven of 44 assessed

patients (16%). Grade 3 and 4 neutropenia were observed in 37% and 30% of patients with one episode of febrile neutropenia. The most common drug-related non-hematological toxic effects reported were cutaneous, with 22% and 6% of patients reporting grade 2 and 3 skin rash, respectively and 4% grade 2 hand-foot syndrome. CONCLUSION: Troxacitabine administered by a bolus daily x5 monthly regimen has modest activity in advanced pancreatic adenocarcinoma.

Laquente, B., C. Lacasa, et al. (2008). "Antiangiogenic effect of gemcitabine following metronomic administration in a pancreas cancer model." Mol Cancer Ther **7**(3): 638-47.

Gemcitabine shows a marked antitumor effect as a result of its cytotoxic action toward proliferative cells. In this article, we aim to investigate the potential antitumor and antiangiogenic effect of gemcitabine following a metronomic schedule that involves the regular administration of cytotoxic drugs at doses lower than standard treatment. In vitro results showed that human endothelial cells are more sensitive to gemcitabine (IC(50) 3 nmol/L) than pancreatic tumor cells (IC(50) 20 nmol/L). For in vivo studies, we used an orthotopic implantation model of human pancreatic carcinoma in nude mice. Gemcitabine was administered i.p. following a low-dose schedule (1 mg/kg/d for a month) and compared with the conventional schedule (100 mg/kg days 0, 3, 6, and 9 postimplantation). Metronomic treatment effect on established tumor was equivalent to standard administration. The measure of CD31 endothelial marked area allowed us to show an in vivo antiangiogenic effect of this drug that was further enhanced by using metronomic administration. This effect correlated with an induction of thrombospondin-1, a natural inhibitor of angiogenesis. Our results allow us to hypothesize that, in addition to a direct antiproliferative or cytotoxic antiendothelial cell effect, a secondary effect involving thrombospondin-1 induction might provide an explanation for the specificity of the effects of metronomic gemcitabine treatment.

Lasserre, C., C. Colnot, et al. (1999). "HIP/PAP gene, encoding a C-type lectin overexpressed in primary liver cancer, is expressed in nervous system as well as in intestine and pancreas of the postimplantation mouse embryo." Am J Pathol **154**(5): 1601-10.

We originally isolated the HIP/PAP gene in a differential screen of a human hepatocellular carcinoma cDNA library. This gene is expressed at high levels in 25% of primary liver cancers but not in nontumorous liver. HIP/PAP belongs to the family of C-type lectins and acts as an adhesion molecule for hepatocytes. In normal adult human tissues, HIP/PAP expression is found in pancreas (exocrine and endocrine cells) and small intestine (Paneth and neuroendocrine cells). In order to gain insight into the possible role of HIP/PAP in vivo, we have investigated the pattern of HIP/PAP expression in the developing postimplantation mouse embryo by in situ hybridization. Detailed analysis of developing mouse embryos revealed that HIP/PAP gene exhibits a restricted expression pattern during development. Thus, HIP/PAP transcripts are first observed within the nervous system from day 14.5 onwards in trigeminal ganglia, dorsal root ganglia, and spinal cord where it appears to be an early specific marker of a subpopulation of motor neurons. At laster stages, HIP/PAP transcripts were detected in intestine and pancreas at day 16.5 but not in embryonic liver. This highly restricted expression pattern suggests that HIP/PAP might participate in neuronal as well as intestinal and pancreatic cell development.

Lewis, B. C. (2006). "Development of the pancreas and pancreatic cancer." Endocrinol Metab Clin North Am **35**(2): 397-404, xi.

The pancreas is specified during embryonic development from the gut endoderm. Among the signaling pathways required for the proper development of the organ are the notch and hedgehog signaling pathways. Both of these pathways are reactivated in pancreatic cancers, and sustained hedgehog signaling is required for the viability of most pancreatic cancer cell lines. Further, mouse models of the disease show activation of these pathways, and expression of pancreas progenitor markers. These findings indicate that developmentally regulated gene expression programs are important in the pathogenesis of pancreatic cancer.

Lin, Y., P. S. Goedegebuure, et al. (2006). "Proteins associated with disease and clinical course in pancreas cancer: a proteomic analysis of plasma in surgical patients." J Proteome Res **5**(9): 2169-76.

New biomarkers for pancreas cancer are needed to improve its detection and management. We surveyed the plasma of patients undergoing surgical resection to identify proteins which change in abundance after complete resection of tumor. Using longitudinally collected specimens from surgical patients, we control for normal inter-individual variation which can confound cross-sectional analysis. Recent refinements in two-dimensional gel electrophoresis allowed us to quantify changes in low abundance plasma proteins with precision. To circumvent the traditional limitations of image analysis in comparing two-dimensional gels, we used fluorometric two-dimensional difference gel

electrophoresis to resolve the proteins from pre- and post-surgical plasma from each patient on one physical gel. Furthermore, we increased the ability of our assay to detect low-abundance proteins by depleting the plasma of 12 high-abundance proteins with a multi-affinity column. Informative protein spots from 20 plasma samples across 10 patients were submitted for identification with mass-spectrometry. We identified a group of proteins which change consistently in plasma following complete resection of pancreas tumor. Furthermore, we identified proteins which correlate with post-surgical rapid recurrence of disease. With further identification and validation, the candidate biomarkers which we identify in this study may prove to be useful in the diagnosis, management and prognostication of patients with pancreas cancer.

Liu, T., S. M. Gou, et al. (2007). "Pancreas duodenal homeobox-1 expression and significance in pancreatic cancer." World J Gastroenterol **13**(18): 2615-8.

AIM: To study the correlations of Pancreas duodenal homeobox-1 with pancreatic cancer characteristics, including pathological grading, TNM grading, tumor metastasis and tumor cell proliferation. METHODS: Reverse transcriptase-polymerase chain reaction (RT-PCR) was used to detect PDX-1 mRNA expression in pancreatic cancer tissue and normal pancreatic tissue. The expression of PDX-1 protein was measured by Western blot and immunohistochemistry. Immunohistochemistry was also used to detect proliferative cell nuclear antigen (PCNA). Correlations of PDX-1 with pancreatic cancer characteristics, including pathological grading, TNM grading, tumor metastasis and tumor cell proliferation, were analyzed by using c2 test. RESULTS: Immunohistochemistry showed that 41.1% of pancreatic cancers were positive for PDX-1 expression, but normal pancreatic tissue except islets showed no staining for PDX-1. In consistent with the result of imunohistochemistry, Western blot showed that 37.5% of pancreatic cancers were positive for PDX-1. RT-PCR showed that PDX-1 expression was significantly higher in pancreatic cancer tissues than normal pancreatic tissues (2(-3.56 +/- 0.35) vs 2(-8.76 +/- 0.14), $P < 0.01$). Lymph node metastasis ($P < 0.01$), TNM grading ($P < 0.05$), pathological grading ($P < 0.05$) and tumor cell proliferation ($P < 0.01$) were significantly correlated with PDX-1 expression levels. CONCLUSION: PDX-1 is re-expressed in pancreatic cancer, and PDX-1-positive pancreatic cancer cells show more malignant potential compared to PDX-1-negative cells. Therefore, PDX-1-positive cells may be tumor stem cells and PDX-1 may act as alternate surface marker of pancreatic cancer stem cells.

Luo, J., W. Ye, et al. (2007). "Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study." Lancet **369**(9578): 2015-20.

BACKGROUND: Although classified as carcinogenic, snuff is used increasingly in several populations. Scandinavian moist snuff (snus) has been proposed as a less harmful alternative to smoking, but precise data on the independent associations of snus use with site-specific cancers are sparse. We aimed to assess the risks for cancer of the oral cavity, lung, and pancreas. METHODS: Detailed information about tobacco smoking and snus use was obtained from 279 897 male Swedish construction workers in 1978-92. Complete follow-up until end of 2004 was accomplished through links with population and health registers. To distinguish possible effects of snus from those of smoking, we focused on 125 576 workers who were reported to be never-smokers at entry. Adjusted relative risks were derived from Cox proportional hazards regression models. FINDINGS: 60 cases of oral, 154 of lung, and 83 of pancreatic cancer were recorded in never-smokers. Snus use was independently associated with increased risk of pancreatic cancer (relative risk for ever-users of snus 2.0; 95% CI 1.2-3.3, compared with never-users of any tobacco), but was unrelated to incidence of oral (0.8, 95% CI 0.4-1.7) and lung cancer (0.8, 0.5-1.3). INTERPRETATION: Use of Swedish snus should be added to the list of tentative risk factors for pancreatic cancer. We were unable to confirm any excess of oral or lung cancer in snus users.

Maehara, Y., H. Oiwa, et al. (2000). "Prognosis and surgical treatment of gastric cancer invading the pancreas." Oncology **59**(1): 1-6.

The clinicopathologic characteristics of gastric cancer invading the pancreas have not been determined. Gastrectomy was performed in 282 patients with gastric cancer invading adjacent organs at the Department of Surgery II, Kyushu University Hospital, between 1970 and 1987, and patient data were retrospectively analyzed using univariate and multivariate analyses. Of these patients, 150 (53.2%) had tumors invading the pancreas and 132 had tumors invading adjacent organs other than the pancreas. In both groups, the undifferentiated tissue type with infiltrative growth, lymphatic involvement and lymph node metastasis was common. In cases of pancreas invasion, the extent of lymph node metastasis was more severe, vascular involvement was more frequent and the rate of concomitant liver metastasis was higher. The survival time of the patients with pancreas invasion was shorter compared to patients with cancer invading other organs, and pancreas involvement was

one of the independent factors predicting a poor prognosis. With respect to surgical treatment of gastric cancer invading the pancreas, the prognosis was better for cases treated with curative surgery and pancreas resection. Of 39 patients treated with partial resection of the pancreas, the tumor had invaded only the capsule of the pancreas in 18 and the pancreas in the other 21. Pancreas-invasive gastric cancer cells are likely to advance via lymphatic and vascular routes and survival time is shorter, but curative resection can improve the survival rate, and perioperative treatment should be appropriately designed.

Maisey, N. R., A. Webb, et al. (2000). "FDG-PET in the prediction of survival of patients with cancer of the pancreas: a pilot study." Br J Cancer **83**(3): 287-93.

Carcinoma of the pancreas is an aggressive tumour with an extremely poor prognosis. Recent studies have shown that chemotherapy can improve survival as well as quality of life. Since the prognosis is generally poor, the identification of early responders to chemotherapy is important to avoid unnecessary toxicity in patients who are not responding. Response assessment by conventional radiographic methods is problematical because treatment induces fibrosis and makes tumour measurements difficult. The aim of this pilot study was to assess 18-fluoro-deoxy-glucose positron emission tomography (FDG-PET) as an early marker of the benefit of chemotherapy. Eleven patients with histologically proven adenocarcinoma of the pancreas were treated with protracted venous infusional 5-fluorouracil (PVI 5-FU) alone or PVI 5-FU and mitomycin C (MMC). FDG-PET scans were performed prior to and at 1 month following the commencement of chemotherapy. FDG uptake was compared with the tumour dimensions measured on a computer tomographic (CT) scan. Patients were followed up for relapse, death and symptomatic response. Three of the 11 patients had no measurable FDG uptake prior to chemotherapy. Of the eight patients who had measurable uptake prior to treatment, seven had a reduction in uptake at 1 month. Six out of the 11 patients had no measurable FDG uptake at 1 month. The overall survival (OS) in these patients ranged from 124 to 1460 days, with a median of 318.5 days. This was superior in comparison to patients who had residual FDG uptake at 1 month (median survival 318.5 days vs 139 days; P = 0.034) and there was a trend to improved symptoms (84% [5/6] vs 20% [1/5]; P = 0.13). There was no statistically significant correlation between best CT response and FDG uptake at 1 month. These results suggest that the absence of FDG uptake at 1 month following chemotherapy for carcinoma of the pancreas is an indicator of improved overall survival. This suggests that FDG-PET may be superior to response assessment by conventional radiographic methods and FDG-PET may have the potential to help make difficult treatment decisions in the management of pancreatic cancer. Larger prospective studies are required to confirm this finding.

Malfertheiner, P. and K. Schutte (2006). "Smoking--a trigger for chronic inflammation and cancer development in the pancreas." Am J Gastroenterol **101**(1): 160-2.

Tobacco smoke, with its complexity of constituents, damages the pancreatic organ in multiple ways. Smoke not only affects pancreatic secretion patterns via its nicotine content but induces inflammatory reactions and exerts carcinogenic effects by several other constituents. Smoke enhances ethanol-induced pancreatic injury and accelerates the development and progression of chronic pancreatitis independent of etiology. Through the process of inflammation, smoking contributes to pancreatic carcinogenesis. The experiment of Wittel and colleagues published in this issue of the American Journal of Gastroenterology sheds further light on this topic by reporting in great detail two different kinds of pancreatic damage in rats exposed to high doses of smoke.

Martin, R. F. and R. L. Rossi (2000). "Multidisciplinary considerations for patients with cancer of the pancreas or biliary tract." Surg Clin North Am **80**(2): 709-28.

The past century has been nearly all of the growth in knowledge about the anatomy and pathophysiology associated with cancers of the pancreas and surrounding biliary structures. Through advances in imaging technology, endoscopic practice, improvement in surgical technique and perioperative care, anesthesia advances, and a better appreciation for the usefulness of adjuvant chemotherapy and radiation therapy, physicians can offer patients some hope for long-term survival and a better quality of life when they are faced with these devastating tumors. Although surgical intervention is the "last best hope" for these patients, advances in the nonoperative disciplines will be required for substantial further improvement in patient outcomes.

Martinenghi, S., G. Dell'Antonio, et al. (1997). "Cancer arising after pancreas and/or kidney transplantation in a series of 99 diabetic patients." Diabetes Care **20**(3): 272-5.

OBJECTIVE: Recipients of solid organ transplants have an increased risk of developing certain types of malignancies as compared with the general population. The majority of the literature has

reported on neoplasms in kidney and heart transplant recipients. RESEARCH DESIGN AND METHODS: We describe 9 neoplasms occurring in 7 out of 73 IDDM patients after simultaneous pancreas and kidney transplantation. No cases were recorded among 26 IDDM recipients of kidney transplantation. RESULTS: Among the neoplasms found were 2 cases of posttransplant lymphoproliferative disorder (PTLD), malignant melanoma, basal-cell and squamous-cell carcinoma of the skin in the same patient, squamous-cell carcinoma in situ of the vulva, hepatocarcinoma, small-cell lung cancer, and ductal carcinoma of the breast. Four patients died. Among immunological risk factors, over-immunosuppression for steroid-resistant kidney rejection was administered only in the 2 cases of PTLD. CONCLUSIONS: Increased dosage of immunosuppressive agents may be necessary in some patients of prevent or treat rejection in view of their reduced survival on hemodialysis.

Matsubara, N., H. Baba, et al. (2007). "Rectal cancer metastasis to the head of the pancreas treated with pancreaticoduodenectomy." J Hepatobiliary Pancreat Surg **14**(6): 590-4.

We report a case of a 50-year-old man who developed metastatic pancreatic cancer from a primary rectal cancer that had been curatively removed 3 years previously. The patient presented with a tumor that occupied the head of the pancreas, associated with obstructive jaundice, but the main pancreatic duct was not dilated. The patient was initially diagnosed as having primary pancreatic cancer. Cytological examination of the bile was conclusive for the presence of adenocarcinoma. The patient refused surgical treatment and chose to have gemcitabine therapy (1000 mg/body), which was given 27 times over 10 months. For 1 year, local disease progression was slow and no distant metastases developed; therefore, the initial diagnosis of pancreatic cancer was questioned. At that time, the patient asked for the tumor to be removed, and pancreaticoduodenectomy was performed. On histology, including immunohistochemical staining for cytokeratin 20 (positive) and cytokeratin 7 (negative), the tumor was shown to be a metastatic pancreatic carcinoma that had originated from the original rectal cancer.

Matsuoka, H., Y. Shibamoto, et al. (2000). "In vivo efficacy and pharmacokinetics of a new hypoxic cell radiosensitizer doranidazole in SUIT-2 human pancreatic cancer xenografted in mouse pancreas." Oncol Rep **7**(1): 23-6.

A new 2-nitroimidazole radiosensitizer doranidazole is now undergoing clinical evaluation in combination with intraoperative radiotherapy for unresectable pancreatic cancer. However, there have been no laboratory data on its effect against pancreatic cancer. This study was undertaken to clarify the efficacy and pharmacokinetics of doranidazole in a human pancreatic cancer SUIT-2 xenografted in the pancreas of nude mice. The tumor-bearing mice were irradiated to the upper abdomen using electron beams with or without prior administration of doranidazole. The tumors were excised 3-6 days later and their weight was measured. Doranidazole given alone had no antitumor effect, but it had radiosensitizing effects when 100, 150, or 200 mg/kg of the drug was combined with single 5 Gy irradiation. The tumor/serum ratios for doranidazole concentration were 0.3-0.4, but the concentrations in the tumor were similar to those in the surrounding normal pancreas. At doses of 100 mg/kg or higher, concentrations of doranidazole in the pancreatic tumor appeared to be sufficient to obtain definite radiosensitization.

McFarland, E. G., J. A. Kaufman, et al. (1996). "Preoperative staging of cancer of the pancreas: value of MR angiography versus conventional angiography in detecting portal venous invasion." AJR Am J Roentgenol **166**(1): 37-43.

OBJECTIVE: The purpose of this study was to compare contrast-enhanced MR angiography with conventional catheter angiography for detecting portal venous invasion in the preoperative staging of pancreatic cancer, using the surgical confirmation of vascular involvement as the standard of truth. SUBJECTS AND METHODS: MR and conventional angiography were performed in 20 patients with pancreatic carcinoma, with surgical confirmation in all cases. MR angiography was performed at 1.5 T, with coronal (2.9 mm) and axial (6.0 mm) contrast-enhanced breath-hold two-dimensional time-of-flight imaging. Data from each imaging technique were collected prospectively and analyzed in a blinded fashion by expert vascular radiologists. Vascular involvement in each patient and in each vessel (main portal vein, confluence, splenic vein, and superior mesenteric vein) determined whether the tumor was resectable (normal, abutment) or nonresectable (encased, occluded). Surgical confirmation of the vascular involvement of the portal venous structures was used as the standard of truth in all patients. RESULTS: Among the 20 patients, 11 tumors were surgically resectable and seven were nonresectable with performance of a palliative bypass. MR angiography and conventional angiography had an overall concordance in 65% of patients (13/20; seven resectable, four nonresectable, two false-negatives) on the basis of the vascular status in each patient of the portal venous structures and in 84% (47/56) of the individual vessels surgically confirmed. MR

angiography correctly identified 11 of 11 resectable patients and five of nine nonresectable patients, with four false-negative cases. Conventional angiography correctly identified seven of 11 resectable patients and six of nine nonresectable patients, with three false-negative cases and four false-positive cases. CONCLUSION: The lack of false-positives by MR angiography suggests that MR imaging may provide a noninvasive screen for nonresectability on the basis of vascular involvement, with no patients with potentially resectable tumors being denied surgery by MR angiography in this cohort. However, the presence of false-negatives using MR angiography indicates the procedure would still not fully eliminate unnecessary laparotomies.

Menges, M. and H. W. Pees (1999). "Kaposi's sarcoma of the pancreas mimicking pancreatic cancer in an HIV-infected patient. Clinical diagnosis by detection of HHV 8 in bile and complete remission following antiviral and cytostatic therapy with paclitaxel." Int J Pancreatol **26**(3): 193-9.

BACKGROUND: Diagnosis of pancreatic cancer is usually made by endoscopic retrograde cholangiopancreatography (ERCP) and corresponding findings in computed tomography (CT) or magnetic resonance imaging. Kaposi's sarcoma, a frequent tumor in individuals with a late-stage HIV infection, can be located in the gastrointestinal tract and cause identical symptoms to carcinoma of the same site. A close correlation of this tumor to human herpes virus 8 (HHV 8) has been known for several years and there are reports of successful antiproliferative therapy. METHODS: Aspirated pancreatic juice and bile was investigated for the presence of HHV 8 by polymerase chain reaction. The clinical course of the patient under antiviral therapy and treatment with paclitaxel was studied. RESULTS: A 47-yr-old HIV-infected man with a history of Kaposi's sarcoma of skin and lungs caused by obstructive jaundice in the years before was admitted. ERCP showed a typical double-duct sign and CT revealed a tumorous infiltration of the pancreatic head, highly suspicious for pancreatic adenocarcinoma. A mutation of the ki-ras gene could be ruled out and molecular analysis of bile identified HHV 8 by PCR. Intensive antiviral therapy, including foscarnet and treatment with paclitaxel led to a complete remission within 8 m.o. CONCLUSION: Kaposi's sarcoma of the pancreas possibly mimics pancreatic cancer in HIV-infected subjects. Diagnosis may be made by identification of HHV 8 in pancreatic juice or bile, and successful clinical outcome is possible by intensive antiviral and cytostatic treatment with paclitaxel.

Micke, O., S. Hesselmann, et al. (2005). "Results and follow-up of locally advanced cancer of the exocrine pancreas treated with radiochemotherapy." Anticancer Res **25**(3A): 1523-30.

In locally advanced carcinoma of the exocrine pancreas combined radiochemotherapy has been established as a standard treatment. MATERIALS AND METHODS: Two different treatment schemes have been consecutively used. Between 1/1994 and 12/2001, a total of 110 patients with locally advanced adenocarcinoma of the pancreas were treated with hyperfractionated accelerated radiotherapy to a total dose of 44.8 Gy combined with 5-fluorouracil (5-FU) (600 mg/m2) and folinic acid (FA) (300 mg/m2) injection. Chemotherapy was repeated monthly in non-progressive disease. From 1/2002 to 11/2003, in another 15 consecutive patients, chemotherapy was changed to gemcitabine (Gem) (300 mg/m2) and cisplatinum (Cis) (30 mg/m2), followed by gemcitabine (1000 mg/m2) every 2 weeks in non-progressive patients. RESULTS: Median survival in the 5-FU/FA group was 10.3 months with a 1-year survival of 46.6% and a 2-year survival of 20.1%. Median time to progression was 8.6 months. Treatment was well tolerated with nausea/vomiting grade I/II in 58.2%, grade III/IV in 14.5%, diarrhea grade I/II in 27.3%, leucopenia/thrombopenia grade I/II in 21.8%, grade III/IV in 7.2%, and mucositis grade III/IV in 7.2%. In the Gem/Cis group, median survival was 13.8 months with a 1-year survival of 54.9% and a 2-year survival of 24.4%. The toxicity data also revealed comparable feasibility: nausea/vomiting grade I/II in 46.7%, grade III/IV in 20%, diarrhea grade I/II in 20%, leucopenia/thrombopenia grade I/II in 26. 7%, and grade III/IV in 13.3%. CONCLUSION: Radiochemotherapy in locally advanced pancreatic cancer is an effective and well-tolerated treatment. The long-term efficacy concerning survival is limited. The integration of predictive factors and new chemotherapeutic agents like gemcitabine in the multimodality treatment may give a more promising perspective. Because of the narrow therapeutic index of gemcitabine-based radiochemotherapy schemes, a feasible combination of radiotherapy treatment volume and gemcitabine dose must be found.

Minami, Y., Y. Hasuike, et al. (2008). "Metachronous double cancer of the gallbladder and pancreas associated with pancreaticobiliary maljunction." J Hepatobiliary Pancreat Surg **15**(3): 330-3.

A 50-year-old Japanese woman complained of abdominal and back pain. Ten years previously she had undergone cholecystectomy, choledochectomy, and Roux-en-Y choledochojejunostomy for gallbladder cancer associated with pancreaticobiliary

maljunction without bile duct dilatation. On the present admission, ultrasonography (US) and computed tomography (CT) demonstrated a large mass, 60 mm in size, in the pancreatic tail. Endoscopic retrograde cholangiopancreatography (ERCP) showed obstruction of the main pancreatic duct in the tail of the pancreas and revealed that the pancreatic duct was joined to the bile duct 25 mm above the papilla of Vater. The patient underwent distal pancreatectomy, splenectomy, left adrenalectomy, and partial gastrectomy. Histological examination revealed moderately differentiated ductal adenocarcinoma that had invaded to the proper muscle of the stomach. Double cancer of the gallbladder and pancreas in a patient with pancreaticobiliary maljunction is rare. Although the etiology of cancer of the pancreas associated with pancreaticobiliary maljunction is unclear, we should pay close attention to the pancreas as well as the biliary tract during the long-term follow-up of patients with pancreaticobiliary maljunction after they have undergone a choledochojejunostomy.

Mitsui, S., A. Okui, et al. (2005). "A novel serine protease highly expressed in the pancreas is expressed in various kinds of cancer cells." Febs J **272**(19): 4911-23.

We have isolated a cDNA that encodes a novel serine protease, prosemin, from human brain. The cDNA of human prosemin is 1306 bp, encoding 317 amino acids. It showed significant homology with the sequence of a chromosome 16 cosmid clone (accession no. NT_037887.4). The prosemin gene contains six exons and five introns. The amino acid sequence of prosemin shows significant homology to prostasin, gamma-tryptase, and testisin (43%, 41%, and 38% identity, respectively), the genes of which are also located on chromosome 16. Northern hybridization showed that prosemin is expressed predominantly in the pancreas and weakly in the prostate and cerebellum. However, western blot and RT-PCR analyses showed that prosemin is expressed and secreted from various kinds of cancer cells, such as glioma, pancreas, prostate, and ovarian cell lines. Prosemin is secreted in the cystic fluid of clinical ovarian cancers. Furthermore, immunohistochemistry showed prosemin protein localized in the apical parts of ovarian carcinomas. Recombinant prosemin was expressed in COS cells and was purified by immunoaffinity chromatography. Recombinant prosemin preferentially cleaved benzyloxycarbonyl (Z)-His-Glu-Lys-methylcoumaryl amidide (MCA) and t-butyloxycarbonyl (Boc)-Gln-Ala-Arg-MCA. Our results suggest that prosemin is a novel serine protease of the chromosome 16 cluster that is highly expressed in the pancreas. The usefulness of this serine protease as a candidate tumor marker should be further examined.

Montet, X., R. Weissleder, et al. (2006). "Imaging pancreatic cancer with a peptide-nanoparticle conjugate targeted to normal pancreas." Bioconjug Chem **17**(4): 905-11.

Designing molecules that bind to targets that become upregulated or overexpressed as normal cells become cancerous is an important strategy for both therapeutic and diagnostic drug design. We hypothesized that pancreatic ductal adenocarcinoma (PDAC) might be imaged with the inverse strategy, that is by the design of a nanoparticle-conjugate targeted to bombesin (BN) receptors present on normal acinar cells of the pancreas. Using the fluorescein hapten visualization method to assess the presence of bombesin (BN) receptors, we first demonstrated BN receptors in the normal mouse and human pancreas, but then the lack of BN binding receptors in 13 out of 13 specimens of PDAC. The BN peptide-nanoparticle conjugate, BN-CLIO(Cy5.5), was synthesized and accumulated in the mouse pancreas in receptor dependent fashion, but not in a receptor dependent fashion in other tissues, based on tissue fluorescence measurements. The BN-CLIO(Cy5.5) nanoparticle decreased the T2 of normal pancreas and enhanced the ability to visualize tumor in a model of pancreatic cancer by MRI. The use of BN-CLIO(Cy5.5) nanoparticle as a normal tissue-targeted, T2-reducing contrast agent offers a promising approach to imaging PDAC.

Moore, M. J., J. Hamm, et al. (2003). "Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group." J Clin Oncol **21**(17): 3296-302.

PURPOSE: To compare the selective matrix metalloproteinase inhibitor BAY 12-9566 with the nucleoside analog gemcitabine in the treatment of advanced pancreatic cancer. METHODS: 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/m2 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. RESULTS: 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 3.74 months and 6.59 months, respectively (P <.001; stratified log-rank test). The median progression-free survival for the BAY 12-9566 and gemcitabine arms was 1.68 and 3.5 months, respectively (P <.001). Quality-of-life analysis also favored gemcitabine. CONCLUSION: Gemcitabine is significantly superior to BAY 12-9566 in advanced pancreatic cancer.

Moo-Young, T. A., J. W. Larson, et al. (2009). "Tumor-derived TGF-beta mediates conversion of CD4+Foxp3+ regulatory T cells in a murine model of pancreas cancer." J Immunother **32**(1): 12-21.

CD4+25+Foxp3+ regulatory T cells (Treg) play a critical role in the induction of tolerance to tumor-associated antigens and suppression of antitumor immunity. How Treg are induced in cancer is poorly understood. We reported previously that Treg are significantly elevated in the peripheral blood of patients with pancreas cancer and that in a murine pancreas cancer model induction of Treg seems to be transforming growth factor (TGF)-beta dependent. Here we provide additional evidence that Treg are increased locally within the tumor microenvironment by a mechanism that seems dependent on TGF-beta receptor expression and the presence of tumor derived TGF-beta. The murine pancreas cancer cell line Pan02 produces high levels of TGF-beta both in vitro and in vivo. In contrast, the esophageal murine cancer cell line, Eso2, does not. Immunohistochemical staining of Foxp3 in explanted tumors shows an identifiable population of Treg in the Pan02 (TGF-beta positive) tumors but not Eso2 (TGF-beta negative). Naive CD4+25-Foxp3- T cells, when adoptively transferred into Rag-/- mice, are converted into Foxp3+ Treg in the presence of Pan02 but not Eso2 tumors. Induction of Treg in Pan02 mice is blocked by systemic injection of an anti-TGF-beta antibody. If Rag-/- mice are instead reconstituted with naive CD4+25- T cells expressing a mutated TGF-beta receptor, induction of Foxp3+ Treg in Pan02 bearing mice is blocked. Collectively, these observations further support the role of TGF-beta in the induction of Treg in pancreas adenocarcinoma.

Mulcahy, M. F. (2007). "Adjuvant therapy for pancreas cancer: advances and controversies." Semin Oncol **34**(4): 321-6.

Although the benefit of adjuvant therapy for pancreas cancer is clear, the most effective therapy remains elusive. In the United States, combination therapy with chemotherapy and radiation remains the standard of care, while in other parts of the world the contribution of radiation is questioned. Clinical trials are reported evaluating the benefit of post-resection radiation and chemotherapy with 5-fluoruoracil (5FU), gemcitabine, and combination therapy; chemotherapy alone with either 5FU or gemcitabine; and pre-resection chemotherapy and radiation. Attention to pancreas cancer staging, radiation techniques, and clinical trial design are paramount to interpreting the outcomes from adjuvant therapy. Therapeutic advances will be made with new approaches studied in carefully controlled trials.

Mulcahy, M. F., A. O. Wahl, et al. (2005). "The current status of combined radiotherapy and chemotherapy for locally advanced or resected pancreas cancer." J Natl Compr Canc Netw **3**(5): 637-42.

Pancreas cancer is the fourth most common cause of cancer deaths. Even for the small percentage of patients who can undergo surgical resection of the primary tumor, the risk of recurrence remains unacceptably high. For patients with localized disease that is not amenable to surgical resection, pain related to the primary tumor can significantly impair quality of life. Attempts to improve the duration and quality of life for these patients have included both chemotherapy and radiotherapy. The addition of chemotherapy to radiation may enhance the local effects of radiation or provide treatment of disease outside the radiation field. The results of clinical trials evaluating the appropriate therapy for locally advanced or resected disease have been inconsistent. In some instances, the methods used in these studies became outdated before the results were available. Hopefully, advances in radiation techniques and systemic drug therapy will provide more durable and clinically relevant results. Meanwhile, treatment decisions should be tailored to the clinical situation, including consideration of treatment toxicity and therapy goals. Recognizing which patients are likely to benefit from combination therapy or systemic therapy alone is a subject of future and ongoing clinical trials.

Nagakawa, T., T. Ohta, et al. (1998). "Clinicopathological evaluation of long-term survivors treated for cancer of the head of pancreas." Hepatogastroenterology **45**(23): 1865-9.

BACKGROUND/AIMS: This is a study of 43 patients with cancer of the pancreatic head treated by resection in the past 13 years; 8 patients survived

for 3 years or more and were compared with 17 who died of cancer within 3 years, in terms of histopathological spread. METHODOLOGY: Eight patients with cancer of the pancreatic head who survived for 3 years or more after resection were evaluated clinically. They were compared histologically with 17 patients who died of cancer within 3 years. RESULTS: The long-term survivors had s0 lesion (no frontal invasion of the pancreatic capsule). Lymph node metastasis was absent, or if present, limited to the n1 group. Histological examination showed rpe (positive retroperitoneal invasion) in four of the eight patients (50%). E-ew (-) (no evidence of invasion to the exposed cut surface) was obtained in all patients. They had stage (histological cancer Stage) II or III except for one patient with stage IV. CONCLUSIONS: Based on the results of the evaluation of our patients, the preconditions at present for prolonged survival for patients with cancer of the pancreatic head would appear to be as follows: --no frontal invasion of the pancreatic capsule; --no retropancreatic invasion or no evidence of invasion to the exposed cut surface even if the retroperitoneal tissues are invaded; --no lymph node metastasis or metastasis limited to the first lymph node group.

Nagano, H., K. Koneri, et al. (2009). "Biliopancreatic fistula and abscess formation in the bursa omentalis associated with intraductal papillary mucinous cancer of the pancreas." Int J Clin Oncol **14**(5): 460-4.

We describe an unusual case of biliopancreatic fistula, free perforation, and subsequent abscess formation within the lesser peritoneal sac associated with intraductal papillary mucinous carcinoma (IPMC). A 71-year-old man presented with general fatigue and loss of appetite that had persisted for 1 month. Abdominal computed tomography (CT) revealed findings consistent with an intraductal papillary mucinous neoplasm (IPMN) of the pancreas, accompanied by abscess formation in the bursa omentalis. Gastrointestinal fiberscopy revealed a swollen papilla of Vater expanded by sticky mucus, and a communication between the pancreatic duct and bile duct was demonstrated by the injection of indigo carmine solution into the pancreatic duct. Percutaneous transhepatic abscess drainage (PTAD) was performed on the day of admission. After this procedure, the patient was managed for 1 month and supported nutritionally with glycemic control for diabetes mellitus. After admission, the patient had an episode of obstructive jaundice that was treated by retrograde biliary drainage. Pancreaticoduodenectomy with lymph node dissection was then performed. Pathological examination revealed IPMN with patchy, scattered carcinoma of the pancreatic head and uncinate process with the formation of a biliopancreatic fistula. Bile duct epithelium in the area of the biliopancreatic fistula demonstrated atypical papillary epithelium suggestive of tumor invasion.

Nanashima, A., H. Yamaguchi, et al. (2008). "Hepatectomy and pancreatectomy with combined vascular resection in patients with hepato-biliary and pancreas diseases at a single cancer institute." Hepatogastroenterology **55**(84): 873-8.

BACKGROUND/AIMS: In advanced cancers of hepatobiliary and pancreatic lesions, major vascular resection and reconstruction are necessary to accomplish curative resection, which may provide better patient outcomes. METHODOLOGY: Surgical records, morbidity and mortality, and prognosis were examined in patients with combined vascular resection. Thirty-six patients underwent 18 hepatectomies and 18 pancreatectomies. RESULTS: In 18 patients who underwent hepatic resection, the resected vessels were the portal vein (PV) in 10, vena cava or hepatic vein in 9 and right hepatic artery (RHA) in 3. An artificial graft was used in 2 to replace the vena cava. Vascular bypass was performed in 5 patients. Morbidity was due to biliary stricture in 1 patient and adult respiratory distress syndrome in another who died during hospital stay. Fourteen (82%) had cancer recurrence, of whom 12 died of cancer, one died of other disease, and 2 survived cancer-free. The 5-year survival was 28%. In 18 patients who underwent pancreatectomy, resected vessels were PV in 18 and RHA in 1. An artificial graft was used in 3 and vascular passive bypass was performed in 6. One patient died of sepsis after total pancreatectomy during hospital stay. Eleven (64%) had cancer recurrence, of whom 11 died of cancer, 2 died of other disease, and 4 survived cancer-free. The 3-year survival was 27%. CONCLUSIONS: Complete surgical resection (R0) combined with main vascular resection could be safely performed in many patients with disease of the hepatobiliary and pancreas, which achieved longer survival in some patients even in the advanced stage.

Natsume, T., Y. Watanabe, et al. (2005). "Solitary pancreas metastasis from AFP-producing gastric cancer: report of a case." Hepatogastroenterology **52**(64): 1278-80.

We herein present a case of resected pancreatic metachronous metastasis arising from alpha-fetoprotein-producing gastric cancer. A 75-year-old man underwent distal gastrectomy for alpha-fetoprotein-producing gastric cancer in November 1999. The staging group of TNM classification was Stage IIIA. The serum AFP level normalized after surgical resection. During the follow-up period, it

increased to 42ng/mL in January 2002, and up to 550ng/mL in July 2002: Abdominal computed tomography disclosed a 4-cm mass in the tail of the pancreas and under the diagnosis of pancreas metastasis, distal pancreatectomy with splenectomy was performed. Following this, serum alpha-fetoprotein declined to 61ng/mL, and the postoperative course was uneventful. But it elevated again to 200ng/mL in August, and to 3500ng/mL in September 2002. Computed tomography revealed multiple liver metastases. He was treated with TS-1, but hepatic lesions continued to grow and he died in March 2003. To our knowledge, this case is the first report of resection of solitary pancreas metastasis of alpha-fetoprotein-producing gastric cancer.

Nielsen, S. K., K. Mollgard, et al. (2008). "Characterization of primary cilia and Hedgehog signaling during development of the human pancreas and in human pancreatic duct cancer cell lines." Dev Dyn **237**(8): 2039-52.

Hedgehog (Hh) signaling controls pancreatic development and homeostasis; aberrant Hh signaling is associated with several pancreatic diseases. Here we investigated the link between Hh signaling and primary cilia in the human developing pancreatic ducts and in cultures of human pancreatic duct adenocarcinoma cell lines, PANC-1 and CFPAC-1. We show that the onset of Hh signaling from human embryogenesis to fetal development is associated with accumulation of Hh signaling components Smo and Gli2 in duct primary cilia and a reduction of Gli3 in the duct epithelium. Smo, Ptc, and Gli2 localized to primary cilia of PANC-1 and CFPAC-1 cells, which may maintain high levels of nonstimulated Hh pathway activity. These findings indicate that primary cilia are involved in pancreatic development and postnatal tissue homeostasis.

Nilsson, H. O., U. Stenram, et al. (2006). "Helicobacter species ribosomal DNA in the pancreas, stomach and duodenum of pancreatic cancer patients." World J Gastroenterol **12**(19): 3038-43.

AIM: To determine whether gastric and enteric Helicobacter species are associated with pancreatic cancer. METHODS: Patients with exocrine pancreatic cancer (n = 40), neuroendocrine cancer (n = 14), multiple endocrine neoplasia type 1 (n = 8), and chronic pancreatitis (n = 5) were studied. Other benign pancreatic diseases (n = 10) and specimens of normal pancreas (n = 7) were included as controls. Pancreatic tissue specimens were analyzed by Helicobacter-specific PCR-assay and products were characterized by denaturing gradient electrophoresis and DNA-sequencing. From a subset of the pancreatic cancer patients, gastric and/or duodenal tissue as well as gallbladder and ductus choledochus tissue were analyzed. Gallbladder and choledochus samples were included as controls. Stomach and duodenum samples were investigated to analyze whether a gastric helicobacter might disseminate to the pancreas in pancreatic cancer patients. Pancreatic specimens were analyzed by Bacteroides-specific PCR for detecting the translocation of indigenous gut microbes to the diseased pancreas. RESULTS: Helicobacter DNA was detected in pancreas (tumor and/or surrounding tissue) of 75% of patients with exocrine cancer, 57% of patients with neuroendocrine cancer, 38% of patients with multiple endocrine neoplasia, and 60% of patients with chronic pancreatitis. All samples from other benign pancreatic diseases and normal pancreas were negative. Thirty-three percent of the patients were helicobacter-positive in gastroduodenal specimens. Surprisingly, H. bilis was identified in 60% of the positive gastroduodenal samples. All gallbladder and ductus choledochus specimens were negative for helicobacter. Bacteroides PCR-assay was negative for all pancreatic samples. CONCLUSION: Helicobacter DNA commonly detected in pancreatic cancer suggests a possible role of the emerging pathogens in the development of chronic pancreatitis and pancreatic cancer.

Nishi, M., S. Ohba, et al. (1996). "Dose-response relationship between coffee and the risk of pancreas cancer." Jpn J Clin Oncol **26**(1): 42-8.

A case-control study was conducted and previous epidemiological data were reviewed in order to investigate the dose-response relationship between coffee and the risk of pancreas cancer. The case-control study was community-based and was carried out in Hokkaido, Japan, employing 141 patients with pancreas cancer and 282 controls (two for each case) matched for sex, age and place of residence. The dose-response relationship between coffee (cups/day) and the relative risk of this disease formed a U-shaped curve. The lowest relative risks (0.18 for male and 0.53 for female) were found among "occasional" drinkers. Epidemiological articles published between 1981 and 1993 were selected from Index Medicus using the two key words "coffee" and "pancreas cancer". In many of the previous case-control studies the curve of the dose-response relationship was also U-shaped, when the relative risks were calculated specifically using four or five levels of coffee dose. The nadirs of the relative risks, most of which ranged from 0.5 to 0.7, were found most frequently at small doses (1-2 or 3-4 cups/day). The results of meta-analysis of these studies formed a U-shaped curve. Studies of other types showed almost the same results. Thus it appears that small amounts of coffee might

prevent pancreas cancer, whereas large amounts might cause the disease.

Obana, T., N. Fujita, et al. (2009). "Small pancreatic cancer with pancreas divisum preoperatively diagnosed by pancreatic juice cytology." Intern Med **48**(18): 1661-6.

We present a case of small pancreatic head cancer with pancreas divisum preoperatively diagnosed by pancreatic juice cytology. A 60-year-old woman was referred to our hospital for evaluation of a dilated main pancreatic duct (MPD). A small and poorly reproducible low-echoic lesion in the pancreas was suspected by ultrasonography (US) and endoscopic ultrasonography (EUS). Magnetic resonance cholangiopancreatography (MRCP) failed to visualize the ventral pancreatic duct, and the upstream dorsal pancreatic duct was dilated. Endoscopic retrograde cholangiopancreatography (ERCP) was indicative of pancreas divisum, and complete obstruction of the MPD in the pancreatic head was seen. Cytology of pancreatic juice obtained from the dorsal pancreas after minor papilla sphincterotomy revealed the presence of adenocarcinoma cells. Pancreatoduodenectomy was performed under the diagnosis of pancreatic head cancer with pancreas divisum. Histological examination revealed moderately-differentiated tubular adenocarcinoma 20 mm in diameter, located in the pancreatic head. Dilatation of the dorsal pancreatic duct is sometimes observed in cases with pancreas divisum without the presence of tumors. When pancreatic duct stenosis also exists in such cases, even if a tumor is not clearly visualized by diagnostic imaging, vigorous examinations such as pancreatic juice cytology are recommended to establish an accurate diagnosis.

Ohba, S., M. Nishi, et al. (1996). "Eating habits and pancreas cancer." Int J Pancreatol **20**(1): 37-42.

BACKGROUND: The eating habits of Japanese people are changing, which may have something to do with the increase in pancreas cancer in Japan. METHODS: Chiefly from the viewpoint of the eating habits, we investigated the etiological factors of this cancer through a community-based case-control study, employing 141 cases and 282 controls (two for each case) matched for sex, age, and place of residence, and through an ecologic study using the official reports of food consumption and deaths from this cancer in Hokkaido Prefecture. RESULTS: The case-control study showed that intake of meats and animal viscera increased the risk of this cancer. On the other hand, vegetables and the traditional Japanese foods, e.g., tofu, deep-fried tofu, raw fish, and tempura, reduced the risk. The controls took more of the traditional Japanese foods than the cases. The ecologic study showed there were significantly negative correlations between the annual consumption of plant foods/plant protein and the annual crude mortality of pancreas cancer. CONCLUSION: The traditional Japanese foods, which include many plant foods, are preventive against the occurrence of pancreas cancer.

Ohlund, D., B. Ardnor, et al. (2008). "Expression pattern and circulating levels of endostatin in patients with pancreas cancer." Int J Cancer **122**(12): 2805-10.

Endostatin is a potent inhibitor of angiogenesis that is cleaved from the basement membrane protein type XVIII collagen. Expression of endostatin has recently been shown by Western blot analysis of tissue lysates in normal pancreas and pancreas cancer tissue. We show here that the expression pattern of type XVIII collagen/endostatin is shifted from a general basement membrane staining and is mainly located in the vasculature during tumor progression. This shift in type XVIII collagen/endostatin expression pattern coincides with an up-regulation of MMPs involved in endostatin processing in the tumor microenvironment, such as MMP-3, MMP-9 and MMP-13. The circulating levels of endostatin was analyzed in patients with pancreas cancer and compared to that of healthy controls, as well as after surgical treatment or in a group of nonoperable patients after intraperitoneal fluorouracil (5-FU) chemotherapy. The results show that patients with pancreas cancer have increased circulating levels of endostatin and that these levels are normalized after surgery or intraperitoneal chemotherapy. These findings indicate that endostatin could be used as a biomarker for pancreas cancer progression.

Ohlund, D., C. Lundin, et al. (2009). "Type IV collagen is a tumour stroma-derived biomarker for pancreas cancer." Br J Cancer **101**(1): 91-7.

BACKGROUND: Pancreas cancer is a dreaded disease with high mortality, despite progress in surgical and oncological treatments in recent years. The field is hampered by a lack of good prognostic and predictive tumour biomarkers to be used during follow-up of patients. METHODS: The circulating level of type IV collagen was measured by ELISA in pancreas cancer patients and controls. The expression pattern of type IV collagen in normal pancreas, pancreas cancer tissue and in pancreas cancer cell lines was studied by immunofluorescence and Western blot techniques. RESULTS: Patients with pancreas cancer have significantly increased circulating levels of type IV collagen. In pancreas cancer tissue high levels of type IV collagen expression was found in close proximity to cancer

cells in the tumour stroma. Furthermore, pancreas cancer cells were found to produce and secrete type IV collagen in vitro, which in part can explain the high type IV collagen expression observed in pancreas cancer tissue, and the increased circulating levels in pancreas cancer patients. Of clinical importance, our results show that the circulating level of type IV collagen after surgery is strongly related to prognosis in patients treated for pancreas cancer by pancreatico-duodenectomy with curative intent. Persisting high levels of circulating type IV collagen after surgery indicates a quick relapse in disease and poor survival. CONCLUSION: Our results most importantly show that stroma related substances can be evaluated as potential cancer biomarkers, and thereby underline the importance of the tumour microenvironment also in this context.

Oman, M., S. Lundqvist, et al. (2005). "Phase I/II trial of intraperitoneal 5-Fluorouracil with and without intravenous vasopressin in non-resectable pancreas cancer." Cancer Chemother Pharmacol **56**(6): 603-9.

BACKGROUND: Systemic palliative treatment with chemotherapy against advanced pancreas cancer has low effectiveness despite considerable toxicity. AIM: To investigate the safety, toxicity and tumour response of intraperitoneal 5-Fluorouracil (5-FU) with intravenous Leucovorin and to monitor 5-FU pharmacokinetics in plasma during intraperitoneal instillation with and without vasopressin in patients with non-resectable pancreas cancer. PATIENTS/METHODS: Between 1994 and 2003, 68 patients with non-resectable pancreas cancer TNM stage III and IV, were enrolled to receive intraperitoneal5-FU instillation 750-1500 mg/m2 and intravenous Leucovorin 100 mg/m2 for two days every third week. Tumour response, performance status and toxicity were recorded. Seventeen patients were also treated with intravenous vasopressin 0.1 IU/minute for 180 minutes, during intraperitoneal 5-FU instillation. Area under the curve (AUC) and peak concentration (Cmax) of 5-FU in plasma were analysed. RESULTS: The treatment was well tolerated with minor toxicity. One complete response (54.1+ months) and 2 partial responses were observed. Time to progression was 4.4 months (0.8-54.1+), and median survival was 8.0 months (0.8-54.1+). There was a significant reduction of 5-FU Cmax in plasma the second day of treatment if vasopressin was used (3.4+/-2.5 and 6.1+/-5.4 mumol/l, respectively, $p<0.05$). 5-FU AUC in plasma was not significantly affected by vasopressin either day of treatment. CONCLUSION: Intraperitoneal 5-FU is a safe treatment with low toxicity to patients with non-resectable pancreas cancer. Tumour response was 4.4% and median survival time 8.0 months. Addition of vasopressin did not significantly decrease plasma 5-FU AUC but reduced Cmax on day 2 of treatment.

Osada, S., F. Sakashita, et al. (2008). "Extracellular signal-regulated kinase phosphorylation due to menadione-induced arylation mediates growth inhibition of pancreas cancer cells." Cancer Chemother Pharmacol **62**(2): 315-20.

BACKGROUND: Cytotoxicity of Vitamin K3 (VK3) is indicated to have the same mechanism with oxidative stress (H(2)O(2)). In the present study, we analyzed the differences and/or similarities in the cellular responses to oxidative stress and VK3 to clarify the mechanism of growth inhibition. METHODS: Cell viability was determined by a test method with 3-[4, 5-dimethyl-thiazol]-2, 5-dephenyl tetrazolium bromide (MTT). Expressions of cellular proteins were evaluated by Western blot analysis. RESULTS: The IC50 was calculated to be 47.3 +/- 4.1 microM for VK3 and 2.2 +/- 1.2 microM for H(2)O(2). By Western blot analysis, VK3 or H(2)O(2) was shown to induce rapid phosphorylation of extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinases (JNKs). H(2)O(2)-induced phosphorylation of ERK and JNK was almost complete inhibited by more than 100-muM genistein. VK3-induced JNK phosphorylation was blocked by 100-microM genistein, but ERK phosphorylation was not inhibited completely even if 400-microM genistein was used. H(2)O(2)-induced inhibition of cell proliferation was completely blocked by 400-microM genistein, but the VK3 effect was reduced 72.8 +/- 5.4% by the same concentration of genistein. H(2)O(2)-induced JNK phosphorylation and ERK phosphorylation were inhibited by staurosporine, protein kinase C (PKC) inhibitor. VK3-induced JNK phosphorylation was also blocked, but ERK phosphorylation was not affected. Staurosporine had no effect on VK3- or H(2)O(2)-induced growth inhibition. Treatment with a non-thiol antioxidant agent, catalase, completely abrogated H(2)O(2)-induced JNK and ERK phosphorylation, but a thiol antioxidant, L: -cystein, had no effect on phosphorylation of them. The VK3-induced JNK phosphorylation was inhibited by catalase, but not L: -cystein. But ERK phosphorylation was not inhibited by catalase and was abrogated completely by the thiol antioxidant. Catalase, but not L: -cystein, blocked H(2)O(2)-induced growth inhibition, and L: -cystein, but not catalase, blocked VK3-induced effects on cell proliferation completely. CONCLUSION: VK3-induced ERK phosphorylation occurs by a different mechanism from oxidative stress, and it might have an important role to induce growth inhibition.

Osborne, C., S. A. Bydder, et al. (2006). "Comparison of non-coplanar and coplanar irradiation techniques to treat cancer of the pancreas." Australas Radiol **50**(5): 463-7.

We compared two different techniques of pancreatic irradiation using measures associated with normal tissue complications. Seven consecutive patients with pancreatic cancer were planned for both coplanar and non-coplanar (NCP) external beam radiation treatments, using the same defined anatomical volumes for each patient, in each case. Each pair of plans was then compared using a range of objective criteria. Individual normal tissues were assessed against traditional tolerance limits. Selected dose-points, normal tissue complication probability (NTCP) and equivalent uniform doses (EUD) were also compared, as were indices combining information from individual tissues - total NTCP and total weighted EUD. All individual normal tissues doses were within established tolerance limits. For NCP relative to coplanar planning, NTCP and EUD were lower for all individual tissues in four cases and one case, respectively, i.e. in most cases a benefit to one tissue was offset by detriment to others. Summary measures demonstrated overall benefits for NCP techniques, with the total NTCP in six patients, and with the total weighted EUD in all patients. NCP techniques show potentially useful benefits. We present a new objective measure, the total weighted EUD, which may be particularly useful comparing plans where there are multiple critical tissues.

O'Sullivan, A. W., N. Heaton, et al. (2009). "Cancer of the uncinate process of the pancreas: surgical anatomy and clinicopathological features." Hepatobiliary Pancreat Dis Int **8**(6): 569-74.

BACKGROUND: The clinicopathological features of uncinate process pancreatic cancer (UPPC) are poorly described. Furthermore the anatomy of the uncinate process and its division during surgery are central to pancreaticoduodenectomy for UPPC. We set out to describe the embryology and anatomy of the uncinate process and the clinicopathological features of UPPC. DATA SOURCES: All published case series of UPPC were reviewed and included in this review. RESULTS: The true incidence of UPPC is difficult to quantify, with the reported incidence ranging from 2.5% to 10.7% of pancreatic cancer. There are 5 published series of UPPC including 117 patients, 72 males and 45 females, aged from 45-53 years to 61-84 years. The median survival was 5 or 5.5 months in 3 of the series, 12.1 months in another based only on potentially resectable lesions and 17 months in another based only on resected cases. CONCLUSIONS: The number of reported series of UPPC is limited, with vague symptoms as the predominant presenting features of the disease. The prognosis is poor with synchronous venous resection demonstrating a survival advantage.

Otte, J. M., K. Kiehne, et al. (2000). "C-met protooncogene expression and its regulation by cytokines in the regenerating pancreas and in pancreatic cancer cells." Scand J Gastroenterol **35**(1): 90-5.

BACKGROUND: Activation of the receptor c-met stimulates motility, mitosis, morphogenesis, processes involved in organ regeneration, or progression of malignancies. In the present study we investigated the expression of c-met protein in the regenerating pancreas and characterized the influence of cytokines on c-met expression. METHODS: Acute pancreatitis was induced in rats by cerulein injection. Rat acini and rat and human pancreatic cancer cells were stimulated with interleukin-1alpha (IL-1alpha), IL-6, tumor necrosis factor-alpha (TNF-alpha) or transforming growth factor-beta1 (TGF-beta1). C-met expression was analyzed by means of Western blotting and localization in pancreatic tissue by immunohistochemistry. RESULTS: C-met protein expression was significantly upregulated in the regenerating pancreas and localized in areas of regenerating tissue. Stimulation with cytokines resulted in a two- to threefold increase of c-met expression in vitro. CONCLUSION: Enhanced c-met expression after acute pancreatitis suggests that HGF/met has an important role in pancreatic regeneration, which is probably mediated by cytokines. This regulatory mechanism is also of importance in pancreatic cancer.

Ouchi, K., T. Sugawara, et al. (1998). "Palliative operation for cancer of the head of the pancreas: significance of pancreaticoduodenectomy and intraoperative radiation therapy for survival and quality of life." World J Surg **22**(4): 413-6; discussion 417.

The benefits of a palliative operation and intraoperative radiation therapy (IORT) for survival and quality of life (QOL) of patients with cancer of the head of the pancreas are not clear. Survival and hospital-free survival (HFS), which are considered to be objective indicators of QOL, were studied in 13 patients who underwent palliative pancreaticoduodenectomy (PD) and 32 patients who underwent surgical bypass. Although there was no significant difference in the survival of patients who underwent PD or bypass (median survivals of 9 months and 7 months, respectively), HFS for 3 months or longer was achieved in 84.6% of the patients who underwent PD, which was significantly higher than that of the 53.1% in patients who underwent surgical

bypass ($p < 0.05$). Among TNM stage III patients, a significant difference in survival was observed between surgical bypass associated with IORT and bypass alone ($p < 0.05$); the median survival time of the IORT group was 10 months, whereas that of the control group was 5 months. In addition, HFS of 3 months or longer was achieved in 83.3% of patients who underwent bypass with IORT but in only 25.0% of the patients who underwent surgery alone ($p < 0.01$). The addition of IORT to palliative PD neither prolonged survival nor improved HFS. These results show the beneficial effect of palliative PD on QOL, and the efficacy of IORT for survival and QOL was proved in cases with stage III pancreatic cancer who underwent surgical bypass. For patients subjected to palliative PD, however, IORT is not thought to be beneficial for either survival or QOL.

Overman, M. J., D. Fogelman, et al. (2008). "Aggressive combined modality therapy for recurrent colorectal cancer involving the duodenum and pancreas: a report of 5 cases." Clin Colorectal Cancer **7**(5): 338-42.

We report 5 cases in which the recurrence of colorectal cancer (CRC) presented as a mass involving the duodenum and pancreas. The treatment approach for such recurrences is not standardized, and in particular, the benefits of pancreaticoduodenectomy for such cases are not known. We describe the successful use of aggressive multimodality treatment with chemotherapy, radiation, and en bloc surgical resection. Such trimodality therapy can result in durable palliation of symptoms and long-term survival for patients with recurrent CRC involving the duodenum and pancreas, even when other metastases are present.

Ozaki, K., M. Nagata, et al. (1998). "Isolation and characterization of a novel human pancreas-specific gene, pancpin, that is down-regulated in pancreatic cancer cells." Genes Chromosomes Cancer **22**(3): 179-85.

By means of the differential display method, we isolated a novel human gene that is expressed specifically in pancreas. The cDNA, designated "pancpin," contained an open reading frame of 1,215 nucleotides encoding a 405 amino acid protein, showing a high degree of similarity to serine protease inhibitors belonging to the serpin superfamily. To investigate its possible role in pancreatic carcinogenesis, we looked for genetic alterations of this gene in pancreatic cancer cell lines and primary pancreatic cancer tissues. Expression of pancpin was barely detectable in any of the four pancreatic cancer cell lines examined, and very weak also in 10 of 13 pancreatic cancer tissues. A somatic missense mutation at codon 221 was found in two of 16 primary pancreatic cancers. These findings indicate that down-regulation of pancpin expression may play a significant role in development or progression of pancreatic cancer.

Paciucci, R., G. Berrozpe, et al. (1996). "Isolation of tissue-type plasminogen activator, cathepsin H, and non-specific cross-reacting antigen from SK-PC-1 pancreas cancer cells using subtractive hybridization." FEBS Lett **385**(1-2): 72-6.

We have used subtractive hybridization to isolate cDNAs overexpressed in SK-PC-1 pancreas cancer cells. Forty-five independent clones corresponding to 11 genes were identified. Their expression in cultured pancreas cancer cells, normal pancreas tissue, and normal exocrine pancreas cultures was examined by Northern blotting. cDNA clones can be grouped into two broad categories: (1) those corresponding to genes expressed at high levels both in tumor cell lines and in primary cultures of normal pancreas, but not in normal tissue (i.e. thymosin beta4(3), cytokeratin 18, beta-actin, pyruvate kinase and mitochondrial genes); and (2) those corresponding to genes expressed at high levels in pancreas cancer cultures but not in normal pancreas tissue or cultured cells (i.e. tissue-type plasminogen activator and cathepsin H). The overexpression of these proteases in pancreas cancers suggests that they play a role in the aggressive biological behavior of this tumor.

Paciucci, R., M. Tora, et al. (1998). "The plasminogen activator system in pancreas cancer: role of t-PA in the invasive potential in vitro." Oncogene **16**(5): 625-33.

Plasminogen activators (PAs) play an important role in tumor cell invasion. We have analysed the expression of tissue-type PA (t-PA), urokinase-type PA (u-PA), and their respective receptors, annexin II and u-PAR, in normal and neoplastic cultures of pancreatic cells, as well as in pancreatic tissues, and have examined their role in tumor invasiveness in vitro. Using Northern blotting, Western blotting, and ELISA, t-PA is detected in cultured pancreas cancer cells displaying a well differentiated phenotype but it is undetectable in less differentiated cells and in normal pancreatic cultures. In contrast, u-PA transcripts, protein, and enzymatic activity are detected both in cancer cells and in normal cultures. Higher levels of u-PAR and annexin II are present in cancer cells than in normal cultures and, in SK-PC-1 cells, both receptors are localized in the basolateral membrane. In vitro invasion assays indicate that both t-PA and u-PA contribute to the invasiveness of SK-PC-1 cells through reconstituted extracellular matrix. To determine the relevance of

these studies to pancreas cancer, immunohistochemical assays have been used to examine the expression of t-PA, u-PA, and their receptors in normal and neoplastic tissues. t-PA is absent from normal pancreas and from tumor associated pancreatitis, whereas it is detected in the majority of pancreas cancer tissues (16/17). Annexin II is also overexpressed in some tumors (5/13). u-PAR is overexpressed in most tumor samples examined (14/15), while u-PA is weakly detected in a low number of cases (3/14); both u-PAR and u-PA are overexpressed in areas of tumor associated pancreatitis. Indirect evidences indicate that K-ras and p53 mutated proteins can regulate the expression of PAs. In pancreatic cancer we have found an association between codon 12 K-ras mutations and t-PA expression (P=0.04). These results support the contention that, in the exocrine pancreas, activation of t-PA is more specifically associated to neoplastic transformation and to the invasive phenotype, whereas the induction of u-PA/u-PAR system might be more relevant to inflammatory or non-neoplastic events.

Perez, R. O., R. B. Coser, et al. (2005). "Combined resection of the duodenum and pancreas for locally advanced colon cancer." Curr Surg **62**(6): 613-7.

Colorectal cancer invading adjacent organs is a frequent event occurring in 5.5% to 12% of all colorectal malignancies. Colon cancer directly invading the duodenum and pancreas is rare and may require combined resection of the colon, pancreas, and duodenum, which represents a complex operation with significant morbidity and mortality rates. In this article, a case of a 41-year-old patient with a right colon cancer directly infiltrating the duodenum and head of the pancreas is presented. The patient was treated by radical combined resection of the colon, duodenum, and pancreas. Pathological examination confirmed neoplastic invasion of the adjacent organs and absence of lymph node metastasis (T4N0). The patient recovered uneventfully. Patients with colorectal cancer infiltrating adjacent organs such as the duodenum and the pancreas should be treated by radical en bloc resection of the tumor. This procedure is the preferred treatment strategy because it seems to be associated with improved overall survival rates.

Petersen, M., M. Evert, et al. (2009). "Serous oligocystic adenoma (SOIA) of the pancreas--first reported case of a genetically fixed association in a patient with hereditary non-polyposis colorectal cancer (HNPCC)." Pathol Res Pract **205**(11): 801-6.

Cystic tumor lesions of the pancreas are relatively uncommon. Advances in imaging and pathohistology, including immunohistochemistry, have led to the detection and classification of novel tumor entities. A promoting aspect is the extended indication profile in pancreatic surgery, in particular, because of lower perioperative morbidity and mortality. One of these classified cystic neoplasms of the pancreas is serous oligocystic adenoma (SOIA), a rare and benign tumor lesion. We report on a 41-year-old man with a cystic lesion within the pancreatic head. Therefore, he underwent pylorus-preserving cephal duodenopancreatectomy. Pathohistologic investigation revealed a SOIA. He had a medical history significant for subtotal colectomy because of a synchronous double colonic carcinoma. Both tumor tissue specimens had been characterized for a high level of microsatellite instability (MSI) and loss of hMLH1, as well as for a corresponding germ line mutation in hMLH1 gene, leading to the diagnosis of hereditary non-polyposis associated colon cancer (HNPCC). The case is remarkable since the SOIA revealed MSI and loss of hMLH1 protein in the tumor cells that has never been reported for this tumor type. In addition, there is a rare and extraordinary association between SOIA and HNPCC, which has never been published before, since SOIA, in this case, could have been developed in the setting of HNPCC syndrome.

Philip, P. A., M. Mooney, et al. (2009). "Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment." J Clin Oncol **27**(33): 5660-9.

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality, despite significant improvements in diagnostic imaging and operative mortality rates. The 5-year survival rate remains less than 5% because of microscopic or gross metastatic disease at time of diagnosis. The Clinical Trials Planning Meeting in pancreatic cancer was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee to discuss the integration of basic and clinical knowledge in the design of clinical trials in PDAC. Major emphasis was placed on the enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. Emphasis was also placed on developing rational combinations of targeted agents and the development of predictive biomarkers to assist selection of patient subsets. The development of preclinical tumor models that are better predictive of human PDAC must be supported with wider availability to the research community. Phase III clinical trials should be implemented only if there is a meaningful clinical signal of efficacy and safety in the phase II setting. The emphasis must therefore be on performing well-designed phase II studies with uniform sets of basic entry and evaluation criteria with

survival as a primary endpoint. Patients with either metastatic or locally advanced PDAC must be studied separately.

Pierce, B. L., D. M. Friedrichsen-Karyadi, et al. (2007). "Genomic scan of 12 hereditary prostate cancer families having an occurrence of pancreas cancer." Prostate **67**(4): 410-5.

BACKGROUND: Prostate cancer is a genetically heterogeneous disease. Using the occurrence of other cancers in hereditary prostate cancer (HPC) families is a promising strategy for developing genetically homogeneous data sets that can enhance the ability to identify susceptibility loci using linkage analysis. METHODS: Twelve HPC families with the co-occurrence of adenocarcinoma of the pancreas were selected from the Prostate Cancer Genetic Research Study (PROGRESS). Non-parametric linkage analysis for a prostate/pancreas cancer susceptibility phenotype was performed using 441 genome-wide microsatellite markers. RESULTS: No statistically significant linkage signal was detected in this analysis. The strongest linkage signals, as measured by Kong and Cox LOD score (KC LOD), were observed on chromosomes 2q37.2-q37.3 (KC LOD = 1.01; P = 0.02) and 16q23.2 (KC LOC = 1.05; P = 0.01). CONCLUSIONS: Despite the lack of statistically significant findings, four chromosomal regions, three of which (2q, 16q, 17q) were previously noted as harboring potential susceptibility loci, showed suggestive linkage results in this scan.

Pietrabissa, A., G. Di Candio, et al. (1996). "Laparoscopic Exposure of the Pancreas and Staging of Pancreatic Cancer." Semin Laparosc Surg **3**(1): 3-9.

Laparoscopy combined with laparoscopic contact ultrasonography was recently proposed as a new and effective method for staging and assessment of resectability in pancreatic cancer. In order to limit the occurrence of false-negative findings, the laparoscopic technique should be as close as possible to the equivalent laparotomic procedure. That includes opening of the lesser sac, which is best achieved through an infragastric route, with resulting wide exposure of the pancreatic body and tail. Laparoscopic contact ultrasonography is then performed for the purpose to define tumor limits, study relationships with major vessels, and assess limphnodal invasion. The results of this procedure in a series of 25 patients are discussed in this report. It is concluded that laparoscopic staging of pancreatic cancer is safe and effective in achieving the goal of avoiding unnecessary laparotomies and selecting candidates for surgical resection.

Ping Lu, Y., T. Ishiwata, et al. (2002). "Lumican expression in alpha cells of islets in pancreas and pancreatic cancer cells." J Pathol **196**(3): 324-30.

Lumican is a member of a small leucine-rich proteoglycan family, members of which play an important role in cell migration and proliferation during embryonic development, tissue repair, and tumour growth. Lumican is reported to be overexpressed during the wound healing process in the cornea and in human breast cancer tissues, but its expression and localization in normal pancreas and pancreatic cancer tissues are not known. The present study aimed to clarify the expression of lumican protein and its mRNA in human pancreatic cancer cell lines and their localization in normal and cancerous human pancreatic tissues. Reverse transcription-polymerase chain reaction (RT-PCR) and western blot analysis revealed lumican mRNA and its protein expression in PK-8 and MIA-PaCa-2 human pancreatic cancer cells. The tumour lumican had non- or poorly sulphated polylactosamine side-chains rather than highly sulphated keratan sulphate chains. Immunoreactivity of the lumican protein was localized in alpha cells of islets and stromal tissues of a normal pancreas. In pancreatic cancer tissues, the lumican protein was strongly localized in cancer cells, and in acinar and islet cells in chronic pancreatitis-like lesions adjacent to the cancer cells. It was also localized in fibroblasts and collagen fibres close to cancer cells. Lumican mRNA was expressed in cancer cells, in acinar and islet cells in chronic pancreatitis-like lesions, and in stromal fibroblasts in the pancreatic cancer tissues. This is the first report that lumican is synthesized in endocrine and cancer cells. Lumican protein may play a role in the maintenance of islet cell function in normal pancreas and the lumican protein synthesized by cancer cells, acinar and islet cells, and stromal fibroblasts may play a role in the growth of human pancreatic cancer cells.

Pour, P. M. and B. Schmied (1999). "The link between exocrine pancreatic cancer and the endocrine pancreas." Int J Pancreatol **25**(2): 77-87.

CONCLUSION: Experimental and human studies during 20 years of research in our laboratories point to the importance of pancreatic islets in the development of ductal-type adenocarcinomas. We believe that pancreatic cancer that develops within ducts, but more frequently within islets, derives from pancreatic stem cells that are distributed within the ductal trees and within the islets. BACKGROUND: The histogenesis of pancreatic cancer is still debatable. Ductal, ductular, and acinar cells all have been declared the tumor progenitor cells. Our long-term human and experimental studies indicate that pancreatic ductal adenocarcinomas arise within ductal

cells and islets. Supporting studies are presented in this article. METHODS: Several human studies and experimental studies on Syrian hamsters conducted within the last 20 years were used in this article. Hamster and human islets were established, and their growth and morphologic changes were examined electron microscopically, immunohistochemically, cytogenetically, and molecular biologically. RESULTS: Studies using the hamster pancreatic cancer model showed that most pancreatic adenocarcinomas develop within islets, most probably from stem cells, which are also believed to be the progenitor cells for tumors that develop within ducts. Studies in newly established human and hamster islets culture validated the immense potential of islet cells to differentiate and become malignant. The higher susceptibility of islet cells to become malignant could be related to their high drug-metabolizing enzymes and their high proliferation rate. Dietary studies indicate that the promoting effect of a high-fat diet on pancreatic carcinogenesis is unrelated to the energy intake, but rather is related to its effect on islet cell replication.

Prenzel, K. L., U. Warnecke-Eberz, et al. (2006). "Differential c-erbB-1 and c-erbB-2 mRNA expression in cancer of the pancreas compared with cancer of the papilla of Vater." World J Gastroenterol **12**(3): 437-42.

AIM: We examined quantitative mRNA expression of growth factor receptors (c-erbB-1, c-erbB-2) and the anti-apoptosis gene survivin known to be regulated in pancreatic adenocarcinomas and compared the expression pattern with that in carcinomas of the papilla of Vater. METHODS: Quantitative real-time reverse transcriptase-PCR (QRT-PCR, Taqman) was performed to analyze mRNA expression levels of c-erbB-1, c-erbB-2 and survivin in normal and corresponding tumor samples of 31 pancreatic adenocarcinomas and 8 cancers of the papilla of Vater. RESULTS: The overall median mRNA expression of survivin was significantly increased in both adenocarcinoma of the pancreas ($P<0.01$) and papilla of Vater ($P<0.008$) compared with uninvolved normal control tissue. In pancreatic cancer, expression of c-erbB-1 was significantly decreased compared with the normal pancreatic tissue ($P<0.03$), whereas in the cancer of the papilla of Vater expression of c-erbB-2 was significantly downregulated ($P<0.05$) compared with the paired normal samples. Gene expression was not associated with tumor stage, differentiation or prognosis. CONCLUSION: The common anti-apoptosis gene survivin is overexpressed both in the cancer of the papilla of Vater and pancreas. In contrast, the growth factor receptor genes c-erbB-1 and c-erbB-2 are differentially regulated in both tumor entities adding further evidence that pancreatic cancer is biologically different from the cancer of papilla of Vater.

Pujal, J., G. Capella, et al. (2006). "The Wnt pathway is active in a small subset of pancreas cancer cell lines." Biochim Biophys Acta **1762**(1): 73-9.

Activation of the Wnt pathway plays an important role in the development of a wide variety of tumor types. Two genes involved in the activation of this pathway in tumors are Adenomatous Polyposis Coli (APC) and beta-catenin. Here, we analyze the activity of the Wnt pathway in cultured cells derived from ductal and acinar pancreatic adenocarcinomas using a reporter assay dependent on the activity of the beta-catenin/Tcf4 complex. We find that low-level Wnt activity can be detected in several pancreas cancer lines. High levels of reporter activity were detected exclusively in RWP-1 cells. These cells display nuclear beta-catenin and express a truncated APC protein resulting from a CAA>TAA mutation (Q1303X). Expression of a dominant negative Tcf4 protein inhibited proliferation of RWP-1 cells but not in other lines lacking beta-catenin-dependent reporter activity, supporting the functional relevance of this mutation. Our findings indicate that activation of the Wnt pathway may play a role in a small subset of ductal pancreatic cancers. Alternatively, RWP-1 cells may have been derived from a tumor arising in a structure adjacent to the pancreas such as the biliary tract or the Ampulla of Vater. Additional studies on the role of Wnt pathway components in the development/progression of tumors of the peripancreatic region merit consideration.

Raimondo, M., I. Tachibana, et al. (2002). "Invasive cancer and survival of intraductal papillary mucinous tumors of the pancreas." Am J Gastroenterol **97**(10): 2553-8.

OBJECTIVES: Intraductal papillary mucinous tumor (IPMT) is frequently associated with pancreatic cancer. We hypothesized that IPMT progresses to invasive cancer with K-ras mutations as an early event, and that invasive cancer affects survival. We compared survival after resection and determined whether K-ras mutations predicted survival in IPMT patients without or with invasive cancer. METHODS: Records of 47 patients with IPMT who were seen between 1983 and 1998 were reviewed retrospectively in 15 cases and prospectively in 32. All histological material was reviewed to confirm the diagnosis of IPMT and to assess invasion. Kaplan-Meier survival curves were analyzed by the log-rank test. The chi2 test was used for differences in K-ras between groups. RESULTS: There were 30 men and 17 women, with a mean age of 65 yr (range 36-90

yr). Of the patients, 26 had IPMT without invasive cancer and 19 had IPMT with invasion. Tissue diagnosis was available in 45 patients. K-ras was analyzed in 40 patients. Mutations were present in 15 of 23 patients (65%) without invasive cancer and in 14 of 17 patients (82%) with invasive cancer (p = ns). At 2.5 yr, the overall cumulative survival of IPMT patients without invasive cancer was 94% compared to 24% of patients with invasive cancer (p < 0.001). The 5-yr survival of IPMT patients without invasive cancer was 94%. K-ras mutations did not correlate with survival. CONCLUSIONS: Invasive cancer in IPMT reduces the 2.5-yr survival after surgery from 93% to 24%. K-ras mutations occur before invasive cancer, and do not predict postoperative survival.

Rosch, T., H. J. Dittler, et al. (2000). "Endoscopic ultrasound criteria for vascular invasion in the staging of cancer of the head of the pancreas: a blind reevaluation of videotapes." Gastrointest Endosc **52**(4): 469-77.

BACKGROUND: It has been claimed in several prospective studies that endoscopic ultrasonography (EUS) is highly accurate in the locoregional staging of pancreatic cancer. However, the value of the EUS criteria for the diagnosis of vascular involvement is less well established. To totally exclude potential bias introduced by the availability of prior information, a completely blinded analysis of videotapes of patients with cancer of the pancreatic head was therefore conducted. METHODS: Videotape sequences of 75 patients with cancer of the head of the pancreas with surgical confirmation or unequivocally positive angiography demonstrating vascular invasion were reevaluated without any clinical data or information from other imaging studies. Involvement of the vascular system (portal vein with confluence, superior mesenteric vein, celiac axis) was assessed on EUS with special emphasis on EUS parameters of the tumor-vessel relationship. RESULTS: The overall sensitivity and specificity of EUS in the diagnosis of venous invasion were 43% and 91%, respectively, when using predetermined parameters (visualization of tumor in the lumen, complete obstruction, or collateral vessels). If the parameter "irregular tumor-vessel relationship" had been added to these criteria, the sensitivity would have risen to 62%, but the specificity would have fallen to 79%. The only vascular system that could be properly visualized by EUS was the portal vein/confluence area. The positive and negative predictive values for the single parameters chosen to diagnose portal venous involvement were as follows: 42% and 33% for irregular tumor-vessel relationship, 36% and 34% for visualization of tumor in the vascular lumen, 80% and 28% for complete vascular obstruction, and 88% and 18% for collateral vessels. CONCLUSIONS: In a completely blinded evaluation of the EUS diagnosis of vascular invasion by cancer of the head of the pancreas it was not possible to find suitable morphologic parameters with clinically useful sensitivity and specificity values (over 80%).

Rothenberg, M. L., M. J. Moore, et al. (1996). "A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer." Ann Oncol **7**(4): 347-53.

PURPOSE: To assess the effect of gemcitabine in patients with metastatic pancreas cancer that had progressed despite prior treatment with 5-FU. PATIENTS AND METHODS: Seventy-four patients were enrolled in this multicenter trial. Alleviation of cancer-related symptoms was the primary endpoint. Sixty-three patients completed a pain stabilization period and were treated with gemcitabine. Clinical Benefit Response was defined as a > or = 50% reduction in pain intensity, > or = 50% reduction in daily analgesic consumption, or > or = 20 point improvement in KPS that was sustained for > or = 4 consecutive weeks. RESULTS: Seventeen of 63 pts (27.0%) attained a Clinical Benefit Response (95% CI: 16.0%-38.0%). The median duration of Clinical Benefit Response was 14 weeks (range: 4-69 weeks). Median survival for patients treated with gemcitabine was 3.85 months (range: 0.3-18.0+ months). Therapy was generally well-tolerated with a low incidence of grade 3 or 4 toxicities. CONCLUSION: Systematic assessment of subjective outcomes can be used to evaluate the clinical impact of new therapies for pancreas cancer, a highly symptomatic disease. Our findings suggest that gemcitabine is a useful palliative agent in patients with 5-FU-refractory pancreas cancer.

Ryschich, E., G. Huszty, et al. (2004). "Transferrin receptor is a marker of malignant phenotype in human pancreatic cancer and in neuroendocrine carcinoma of the pancreas." Eur J Cancer **40**(9): 1418-22.

Transferrin receptor (TFRC) is a membrane-bound protein expressed in larger amounts in proliferating, e.g., malignant, cells than in quiescent cells. The specific expression of TFRC can represent a diagnostic tool or a therapeutic target in solid tumours expressing this antigen. Whether TFRC is expressed in human pancreatic tumours is unknown. The aim of this study was the investigation of the expression of TFRC and transferrin in human pancreatic cancer and in neuroendocrine tumours of the pancreas. Fifty one specimens of human pancreatic cancer and 14 samples of pancreatic neuroendocrine tumours were obtained after surgery. The expression of TFRC, transferrin and cytokeratin was studied by standard immunohistochemistry. Flow cytometry was used for

the investigation of TFRC expression in nine cell lines of ductal pancreatic cancer in vitro. In contrast to normal tissue, 93% of pancreatic tumour cells showed positive (82%) or heterogeneous (11%) expression of TFRC. It was strongly expressed by malignant epithelial cells; normal stromal and endothelial cells were not stained by anti-TFRC antibodies. Primary tumours and metastases showed a similar frequency of TFRC expression. Three neuroendocrine carcinomas showed positive expression of TFRC by malignant tumour cells. The expression of TFRC was negative in benign neuroendocrine tumours of the pancreas. The cell lines of pancreatic cancer were characterised by a low expression of TFRC in vitro. In contrast to normal pancreatic tissue and benign neuroendocrine tumours of the pancreas, pancreatic cancer and neuroendocrine carcinoma are therefore characterised frequently by high expression of TFRC. Hence, TFRC represents a marker of malignant transformation in the pancreas that could be applied as potential diagnostic and therapeutic target.

Sakuramoto, S., S. Kikuchi, et al. (2009). "Laparoscopy-assisted pancreas- and spleen-preserving total gastrectomy for gastric cancer as compared with open total gastrectomy." Surg Endosc **23**(11): 2416-23.

BACKGROUND: Laparoscopy-assisted total gastrectomy (LATG) is not widely used for the treatment of gastric cancer located in the upper or middle third of the stomach. To assess the safety and usefulness of LATG, we compared the outcomes of LATG with those of open total gastrectomy (OTG). METHODS: From July 2004 to July 2007, we performed pancreas- and spleen-preserving total gastrectomy with D1 + beta or D2 lymph-node dissection and Roux-en-Y reconstruction in 74 patients with cancer located in the upper or middle third of the stomach. Of these patients, 30 underwent LATG (LATG group) and 44 underwent OTG (OTG group). Short-term outcomes were compared between the groups. RESULTS: Operation time was significantly longer in the LATG group than in the OTG group (313 min vs. 218 min, $p < 0.001$). Blood loss (134 g vs. 407 g, $p < 0.001$) and the rate of the use of analgesics (6.8 times vs. 11.8 times, $p < 0.05$) were significantly lower, and postoperative hospital stay was significantly shorter in the LATG group than in the OTG group (13.5 days vs. 18.2 days, $p < 0.05$). The LATG group had better hematologic and serum chemical profiles, including white-cell counts, C-reactive protein levels, total protein levels, and albumin levels, as well as lower rate of postoperative body-weight loss. The number of dissected lymph nodes (43.2 vs. 51.2, $p = 0.098$) and the rate of postoperative complications (20.0% vs. 27.3%, $p = 0.287$) were similar in the groups. However, major complications such as anastomotic leakage, abdominal abscess, and pancreatic leakage occurred in six patients (13.6%) in the OTG group, but in none of the patients in the LATG group. CONCLUSIONS: LATG is associated with less severe complications and better postoperative quality of life than OTG. We believe that LATG is a safe, useful, and less invasive alternative for the treatment of gastric cancer located in the upper or middle third of the stomach.

Sasson, A. R., J. P. Hoffman, et al. (2002). "En bloc resection for locally advanced cancer of the pancreas: is it worthwhile?" J Gastrointest Surg **6**(2): 147-57; discussion 157-8.

The benefit of radical surgical resection of contiguously involved structures for locally advanced pancreatic cancer is unclear. The aim of this study was to examine patient outcome after extended pancreatic resection for locally advanced tumors and to determine if any subset of extended resection affected outcome. We retrospectively reviewed the records of 116 patients with adenocarcinoma of the pancreas, who underwent extirpative pancreatic surgery between 1987 and 2000. Of the 116 patients, 37 (32%) required resection of surrounding structures (group I), and 79 patients (68%) underwent standard pancreatic resections (group II). In all cases, all macroscopic disease was excised. In group I a total of 46 contiguously involved structures were resected: vascular in 25 patients (54%), mesocolon in 16 (35%) (colic vessels in 3, colon in 13), adrenal in three (7%), liver in one (2%), stomach in one (2%) (for a tumor in the tail of the pancreas), and multiple structures in four. Excision of regional blood vessels included the superior mesenteric vein and/or portal vein in 16, hepatic artery in five, and celiac axis in four. No differences between groups I and II were detected for any of the following parameters: age, sex, history of previous operation, estimated blood loss, or hospital stay. For the entire cohort the morbidity and mortality were 38% and 1.7%, respectively, and these rates were similar in the two groups. Adjuvant therapy was administered to more than 90% of patients in both groups. However, patients in group I were more likely to have received neoadjuvant therapy (76% vs. 42%, $P = 0.001$). Total pancreatectomy and distal pancreatectomy were more often performed in group I ($P = 0.005$). Additionally, the median operative time was longer (8.5 hours compared to 6.9 hours ($P = 0.0004$)). Both groups had similar rates of microscopically positive margins and involved lymph nodes, as well as total number of lymph nodes removed. The median survival was 26 months for patients in group I and 16 months for patients in group II ($P = 0.08$). The median disease-free survival for

groups I and II was 16 months and 14 months, respectively (P = 0.88). In comparing patients in group I, who underwent vascular resection vs. mesocolon (colon or middle colic vessels) resection, the median survival was 26 months and 19 months, respectively (P = 0.12). We were unable to detect a difference in outcome for patients with locally advanced cancers requiring extended pancreatic resections compared to patients with standard resections. En bloc resection of involved surrounding structures, to completely extirpate all macroscopic disease, may be of benefit in selected patients with locally advanced disease, particularly when combined with preoperative chemoradiation therapy.

Savinov, A. Y., D. V. Rozanov, et al. (2005). "Inhibition of membrane type-1 matrix metalloproteinase by cancer drugs interferes with the homing of diabetogenic T cells into the pancreas." J Biol Chem **280**(30): 27755-8.

We have discovered that clinically tested inhibitors of matrix metalloproteinases can control the functional activity of T cell membrane type-1 matrix metalloproteinase (MT1-MMP) and the onset of disease in a rodent model of type 1 diabetes in non-obese diabetic mice. We determined that MT1-MMP proteolysis of the T cell surface CD44 adhesion receptor affects the homing of T cells into the pancreas. We also determined that both the induction of the intrinsic T cell MT1-MMP activity and the shedding of cellular CD44 follow the adhesion of insulin-specific, CD8-positive, Kd-restricted T cells to the matrix. Conversely, inhibition of these events by AG3340 (a potent hydroxamate inhibitor that was widely used in clinical trials in cancer patents) impedes the transmigration of diabetogenic T cells into the pancreas and protects non-obese diabetic mice from diabetes onset. Overall, our studies have divulged a previously unknown function of MT1-MMP and identified a promising novel drug target in type I diabetes.

Schlieman, M. G., B. N. Fahy, et al. (2003). "Incidence, mechanism and prognostic value of activated AKT in pancreas cancer." Br J Cancer **89**(11): 2110-5.

When activated, the serine/threonine kinase AKT mediates an antiapoptotic signal implicated in chemoresistance of various cancers. The mechanism(s) of AKT activation are unknown, though overexpression of HER-2/neu has been implicated in breast cancer. Therefore, we determined the incidence of activated AKT in human pancreatic cancer, whether HER-2/neu is involved in AKT activation, and if AKT activation is associated with biologic behaviour. HER-2/neu expression and AKT activation were examined in seven pancreatic cancer cell lines by Western blotting. The in vitro effect of HER-2/neu inhibition on AKT activation was similarly determined. Finally, 78 pancreatic cancer specimens were examined for AKT activation and HER-2/neu overexpression, and correlated with the clinical prognostic variable of histologic grade. HER-2/neu was overexpressed in two of seven cell lines; these two cell lines demonstrated the highest level of AKT activation. Inhibition of HER-2/neu reduced AKT activation in vitro. AKT was activated in 46 out of 78 (59%) of the pancreatic cancers; HER-2/neu overexpression correlated with AKT activation (P=0.015). Furthermore, AKT activation was correlated with higher histologic tumour grade (P=0.047). Thus, it is concluded that AKT is frequently activated in pancreatic cancer; this antiapoptotic signal may be mediated by HER-2/neu overexpression. AKT activation is associated with tumour grade, an important prognostic factor.

Servais, A., S. R. Pestieau, et al. (2001). "Autoimmune pancreatitis mimicking cancer of the head of pancreas: report of two cases." Acta Gastroenterol Belg **64**(2): 227-30.

Autoimmune pancreatitis has been characterised in 1995, but only a few cases have been published since then, most of them from Japan. This report describes the cases of two Belgian male patients who presented with isolated obstructive jaundice. Radiological imaging studies were highly suggestive of carcinoma of the head of pancreas and both patients underwent uneventful cephalic pancreaticoduodenectomy with portal vein resection. Pathological analysis of the removed tissues suggested an autoimmune process in both cases. Both patients had hyper-gammaglobulinemia and antinuclear antibodies, but failed to show evidence of any other autoimmune disease or cause of chronic pancreatitis. In both cases final diagnosis was autoimmune pancreatitis. Preoperative clinical suspicion of this diagnosis is mandatory and may avoid unnecessary surgery in future cases.

Sperti, C., C. Pasquali, et al. (2009). "Metastasis to the pancreas from colorectal cancer: is there a place for pancreatic resection?" Dis Colon Rectum **52**(6): 1154-9.

PURPOSE: Pancreatic metastases from colorectal cancer are very rare, and the possible benefit of surgical treatment is not clearly defined. This study was designed to evaluate the outcome of patients undergoing pancreatic resection for metastatic colorectal cancer to the pancreas. METHODS: Nine patients underwent pancreatic resection for metastatic colorectal cancer between January 1980 and

December 2006. The primary cancers were colon (n = 7) and rectal carcinoma (n = 2). The median interval between primary treatment and detection of pancreatic metastases was 32.5 months. In three cases pancreatic metastases were synchronous with the primary tumor. RESULTS: Five patients underwent pancreaticoduodenectomy, and four underwent distal pancreatectomy. A left lateral liver section and three colon resections were simultaneously performed in four patients. There was no postoperative mortality, and only two patients experienced complications. Survival averaged 19.8 (median, 17.0; range, 5-30) months: seven patients died of metastatic disease, one for unrelated disease after five months, and one is alive with liver metastases 30 months after surgery. CONCLUSION: Surgical resection can be performed safely in patients with isolated pancreatic metastases from colorectal cancer and in selected patients with associated extrapancreatic disease. Although long-term survival is rare, surgery should be included, whenever possible, in the multimodality approach to this disease.

Spiliotis, J. D., A. C. Datsis, et al. (2007). "Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas." Langenbecks Arch Surg **392**(1): 55-60.

BACKGROUND AND AIM: The aim of this study is to identify the benefit acquired by the use of radiofrequency ablation in parallel to palliative therapy in patients with advanced cancer of the pancreas. MATERIALS AND METHODS: Data on 25 consecutive patients who underwent palliative therapy with or without radiofrequency ablation for unresectable pancreatic cancer were included in this retrospective review. Thirteen patients received palliative therapy alone, whereas 12 patients received palliative therapy plus radiofrequency ablation. RESULTS: Overall mean survival rate in patients receiving paliative therapy alone was 13 months and the maximum survival was 30 months. Where radiofrequency ablation was applied, mean survival was estimated at 33 months (p = 0.0048). Stage III and IV patients treated with palliative therapy alone have a mean survival of 15 and 10 months, respectively. All stage III patients receiving radiofrequency ablation are alive at present and maximum survival has reached 38 months (p = 0.0032), whereas stage IV patients who were treated with radiofrequency ablation have an estimated mean survival period of 14 months (p = 0.1095). CONCLUSION: Radiofrequency ablation in parallel to palliative therapy seems to provide survival benefit especially for stage III patients with unresectable pancreatic cancer. Further studies should be conducted to determine the usefulness of radiofrequency ablation in the treatment of advanced pancreatic cancer.

Sponsiello-Wang, Z., R. Weitkunat, et al. (2008). "Systematic review of the relation between smokeless tobacco and cancer of the pancreas in Europe and North America." BMC Cancer **8**: 356.

BACKGROUND: Recent reviews claiming smokeless tobacco increases pancreatic cancer risk appear not to have considered all available epidemiological evidence; nor were meta-analyses included. We present a systematic review of studies from North America and Europe, since data are lacking from other continents. Risk is also difficult to quantify elsewhere due to the various products, compositions and usage practices involved. METHODS: Epidemiological studies were identified that related pancreatic cancer to use of snuff, chewing tobacco or unspecified smokeless tobacco. Study details and effect estimates (relative risks or odds ratios) were extracted, and combined by meta-analyses. RESULTS: Nine North American and two Scandinavian studies were identified. Reporting was limited in four studies, so only seven were included in meta-analyses, some providing results for never smokers, some for the overall population of smokers and non-smokers, and some for both. Giving preference to study-specific estimates for the overall population, if available, and for never smokers otherwise, the random-effects estimate for ever smokeless tobacco use was 1.03 (95% confidence interval 0.71-1.49) based on heterogeneous estimates from seven studies. The estimate varied little by continent, study type, or type of smokeless tobacco. Giving preference to estimates for never smokers, if available, and overall population estimates otherwise, the estimate was 1.14 (0.67-1.93), again based on heterogeneous estimates. Estimates varied (p = 0.014) between cohort studies (1.75, 1.20-2.54) and case-control studies (0.84, 0.36-1.97). The value for cohort studies derived mainly from one study, which reported an increase for never smokers (2.0, 1.2-3.3), but not overall (0.9, 0.7-1.2). This study also contributed to increases seen for snuff use and for European studies, significant only in fixed-effect analyses. The studies have various weaknesses, including few exposed cases, reliance in cohort studies on exposure recorded at baseline, poor control groups in some case-control studies, and lack of a dose-response. Publication bias, with some negative studies not being presented, is also possible. CONCLUSION: At most, the data suggest a possible effect of smokeless tobacco on pancreatic cancer risk. More evidence is needed. If any risk exists, it is highly likely to be less than that from smoking.

Standop, J., M. Schneider, et al. (2003). "Differences in immunohistochemical expression of xenobiotic-metabolizing enzymes between normal pancreas, chronic pancreatitis and pancreatic cancer." Toxicol Pathol **31**(5): 506-13.

Metabolic activation of many toxins, carcinogens, drugs, and anti-cancer agents is governed by the cytochrome P450 (CYP) drug-metabolizing enzyme system. To help elucidate the role of this enzyme system in the pathogenesis of chronic inflammatory and malignant pancreatic diseases, we compared the immunohistochemical expression pattern of 8 CYP-enzymes in 24 normal, 20 chronic pancreatitis, and 21 pancreatic cancer specimens using antibodies to CYP 1A1, 1A2, 2B6, 2C8/9/19, 2D6, 2E1, and 3A4, and the NADPH cytochrome P450 oxido-reductase (NA-OR). Compared to the normal pancreas, a higher frequency of immunopositivity for CYP 1A2, 2B6, 2C8/9/19, 2D6, and NA-OR was found in chronic pancreatitis, and of all CYPs but 1A2 in pancreatic cancer. On the other hand, CYP 1A1 and 2E1 antibody staining was less frequently observed in chronic pancreatitis. In all specimens with pancreatic polypeptide (PP)-rich regions (pancreas head), more islet cells than ductal and acinar cells were immunopositive. Moreover, the immunoreactivity of islet cells from PP-rich specimens with anti-CYP antibodies was consistently more frequent and intense than in islet cells from PP-poor areas (body and tail). Immunoreactivity for xenobiotic-metabolizing enzymes was frequently observed in the normal pancreas, chronic pancreatitis, and pancreatic cancer, and displayed differences of its frequency and intensity between the 3 groups. Considering immunohistochemical evidence of enzyme expression and pancreatic blood supply together, islet cells appear to be an important and possible early site of CYP-enzyme induction in pancreatic diseases.

Standop, J., M. Schneider, et al. (2004). "ErbB2 oncogene antibodies differentiate between the normal and diseased pancreas, and between chronic pancreatitis and pancreatic cancer." Oncol Rep **12**(6): 1309-15.

Histological differentiation between chronic pancreatitis and pancreatic cancer, especially in biopsy material, remains challenging and the frequent association of 'secondary' chronic pancreatitis (due to ductal obstruction) with pancreatic cancer causes additional diagnostic problems. Our study, using anti-ErbB2 antibodies from Santa Cruz and Dako in tissues from the normal pancreas, chronic pancreatitis and pancreatic cancer showed that these antibodies discriminate between primary chronic pancreatitis and 'secondary' chronic pancreatitis due to pancreatic cancer. Tissues from 28 pancreatic cancer patients, 15 chronic pancreatitis patients and 12 organ donors or early autopsy cases were subjected to immunohistochemical studies using polyclonal ErbB2 antibodies from Santa Cruz and Dako. The Santa Cruz antibody immunoreacted with islet cells in all tissues from the normal pancreas and pancreatic cancer but not in any chronic pancreatitis specimen. The Dako antibody showed a membrane staining of ductal and ductular cells only in chronic pancreatitis cases but in none of the normal or cancer specimens. Moreover, in chronic pancreatitis cases, ductular cells were stained with the Santa Cruz antibody only in the severe form, but not in the mild or moderate form of the disease. The utilized ErbB2 antibodies discriminate between the normal pancreas, chronic pancreatitis and pancreatic cancer. Hence, these antibodies seem to present an additional useful aid in the surgical pathology of pancreatic diseases.

Stanton, K. J., R. A. Sidner, et al. (2003). "Analysis of Ki-67 antigen expression, DNA proliferative fraction, and survival in resected cancer of the pancreas." Am J Surg **186**(5): 486-92.

BACKGROUND: Prognostic markers for pancreas cancer, such as CEA, CA19-9, ploidy analysis, and S-phase determination using flow cytometry, have not been consistently predictive. We chose to evaluate nuclear proliferation, as measured by the MIB-1 monoclonal antibody and digital image analysis, as a prognostic marker in pancreatic carcinoma, and compare the findings with DNA ploidy and S-phase analysis. MIB-1 identifies the Ki67 antigen present in nuclei of cells in all phases of the cell cycle except G0. METHODS: We retrospectively reviewed 33 patients with pancreatic adenocarcinoma resected for cure between 1989 and 1994 with available fixed tissue. Sectioned tissue was stained with MIB-1, and the number of positively stained nuclei determined and expressed as a MIB-1 labeling index (LI) by quantitative image analysis. Disaggregated nuclei were analyzed by flow cytometry using standard techniques. RESULTS: MIB-1 LI for pancreas cancers was heterogeneous within and between cancers. The MIB-1 LI for the cancers was 28 +/- 15 (median 29). There was no correlation between survival and MIB-1 expression (R(2) = 0.03). Likewise, there was no correlation between MIB-1 LI and percentage of cells in S-phase, G(2)/M, or total proliferating cells (S+G(2)/M; R(2) = 0.01), nor was there a difference between MIB-1 LI and ploidy (P = 0.88). CONCLUSIONS: We conclude that in our patient population, nuclear proliferation in pancreatic cancer, as determined by expression of Ki67 nuclear antigen, does not appear to correlate with survival and is not a useful prognostic marker. Despite intuitive thoughts to the contrary, there is no

correlation between cell cycle analysis as determined by flow cytometry and Ki67 expression in pancreas cancer. Current methods of assessing prognosis after curative resection of cancer of the pancreas, including lymph node and margin status, tumor size, and possibly DNA ploidy as determined by flow cytometry, are not augmented by the assessment of nuclear proliferation by image analysis using the MIB-1 monoclonal antibody.

Stephens, F. O. (1999). "The increased incidence of cancer of the pancreas: is there a missing dietary factor? Can it be reversed?" Aust N Z J Surg **69**(5): 331-5.

There has been a disturbing increase in the incidence of pancreas cancer, especially in Western countries, during the present century. The only well-established aetiological factor of well-documented significance is the greater incidence of this cancer in tobacco smokers of all communities. Otherwise the reason for the increased incidence is not known but the pattern of increase has some similarities to the increased incidence of breast cancer in women and prostate cancer in men in Western communities. There is now well-documented evidence that the increase in breast and prostate cancers is at least partly related to diet. Typical modern Western diets have a low content of the naturally occurring plant hormones, the phyto-oestrogens, that are still plentiful in traditional diets of Asians and other communities with a low incidence of both breast and prostate cancer. This paper presents evidence to support the hypothesis that the increased incidence of pancreas cancer in Western communities may also be related to the relatively low dietary content and protective qualities of the naturally occurring plant hormones and related compounds. This paper presents evidence to support that hypothesis.

Stracke, S., L. Ramudo, et al. (2006). "Antiproliferative and overadditive effects of everolimus and mycophenolate mofetil in pancreas and lung cancer cells in vitro." Transplant Proc **38**(3): 766-70.

BACKGROUND: Everolimus inhibits the growth of several tumor cell lines in vitro as well as tumor growth in a rat model. Mycophenolate mofetil (MMF) inhibits growth of a Walker sarcoma in a rat model in vivo. Herein we tested the in vitro antiproliferative capacity of everolimus and MMF on a pancreatic tumor cell line Panc-1 and on a small cell lung cancer cell line ScLc. MATERIALS AND METHODS: Cells were cultured under standardized conditions. Everolimus was added in increasing doses from 0.005 to 500 microg/mL; MMF was used from 0.05 to 5000 microg/mL. For co-incubation experiments, we combined everolimus (0.005 microg/mL and 0.05 microg/mL) with five concentrations of MMF; and MMF (0.5 microg/mL and 5 microg/mL) with five concentrations of everolimus. The antiproliferative capacity was assessed by a BrdU incorporation assay. RESULTS: Everolimus and MMF inhibited BrdU incorporation into Panc-1 and ScLc in a dose-dependent fashion. A 50% inhibition was seen in Panc-1 only at 50 microg/mL everolimus, but in ScLc at 5 microg/mL everolimus. MMF was clearly more potent in Panc-1: 50% inhibition was observed at 5 microg/L. In ScLc, 40% inhibition of BrdU incorporation was seen only at 50 microg/L MMF. In co-incubation, an effective combination for both Panc-1 and ScLc was 5 microg/mL MMF with 0.005 microg/mL everolimus resulting in 50% inhibition of BrdU incorporation ($P < .001$). CONCLUSIONS: Everolimus and MMF showed dose-dependent antiproliferative effects in tumor cell lines in vitro both alone and in combination. The combined use of everolimus and MMF showed supra-additive effects at concentrations used for therapeutic immunosuppression in patients.

Sweeney, A. D., M. F. Wu, et al. (2009). "Value of pancreatic resection for cancer metastatic to the pancreas." J Surg Res **156**(2): 189-98.

BACKGROUND: Cancer metastatic to the pancreas from other primary sites is uncommon, and it has been treated with an aggressive surgical approach in fit patients when the primary tumor is controlled and the pancreas is the only site of metastatic disease. The value of pancreatic resection in this setting is unclear. The purpose of this study was to review cases of cancer metastatic to the pancreas. METHODS: We reviewed our experience with cancer metastatic to the pancreas and the literature regarding resection of pancreatic metastases. Patient and tumor characteristics were summarized using descriptive statistics. RESULTS: A total of 220 patients with pancreatic metastasis were analyzed. Three patients were selected from our own experience, and 217 were selected from a literature review. In the 127 patients whose symptoms were recorded at the time of presentation, the most common presenting symptoms were jaundice (n=32, 25.2%) and abdominal pain (n=25, 19.7%). In the 189 patients for whom the location of the metastasis in the pancreas was revealed, the most common location was the head of the pancreas (n=79, 41.8%). The primary tumor site was most commonly kidney (n=155, 70.5%). Surgical resection was attempted in 177 of 220 patients; 135 patients suffering from renal cell carcinoma (RCC) metastasis also underwent pancreatic resection. In the latter group, a median survival of 70 mo was seen, as well as 78% and 65% 2- and 5 y survival rates,

respectively. CONCLUSION: Survival after resection of RCC with isolated metastasis to the pancreas is favorable. However, a more detailed analysis considering outcomes without surgery for each primary tumor site is needed before the value of this aggressive surgical approach can be completely assessed in the general occurrence of pancreatic metastasis.

Tabata, M., J. Kitayama, et al. (2003). "Autoimmune pancreatitis presenting as a mass in the head of the pancreas: a diagnosis to differentiate from cancer." Am Surg **69**(5): 363-6.

We report a case of autoimmune pancreatitis presenting as a mass in the head of the pancreas that was successfully diagnosed without pancreaticoduodenectomy. The patient was a 64-year-old man who had no complaint. A routine physical checkup unexpectedly revealed mild diabetes and a low-echoic mass in the pancreatic head. The diagnosis was made by noting irregular narrowing of the main pancreatic duct, hypergammaglobulinemia, and increased immunoglobulin G levels. An open wedge biopsy of the mass was performed; this showed a marked fibrosis with lymphocyte- or macrophage-predominant inflammatory infiltrates. Immunohistochemical study revealed that the remnant acinar cells expressed Fas (CD95) ligand and not Fas. We review some of the literature and discuss various features and diagnostic clues of autoimmune pancreatitis. Awareness of this pathologic condition may prevent confusion with pancreatic malignancy and unnecessary surgery.

Takahashi, Y., M. Mai, et al. (2005). "A pilot study of individualized maximum repeatable dose (iMRD), a new dose finding system, of weekly gemcitabine for patients with metastatic pancreas cancer." Pancreas **30**(3): 206-10.

OBJECTIVES: We developed and established a new dose-finding system, the individualized maximum repeatable dose (iMRD), suitable to induce prolonged TTP rather than tumor shrinkage. METHODS: We applied this system in weekly gemcitabine therapy for 18 metastatic pancreas cancer patients. We determined the iMRD at the 5th week, after weekly dose adjustments. We started at 500 mg/m2 (1/2 maximum tolerated dose) of gemcitabine and repeated the treatment with an increase or a decrease of 100 mg/m each week, if toxicity was 0 or more than grade 1, respectively. RESULTS: The iMRD of weekly gemcitabine was 300 mg/m2 in 2 patients, 400 mg/m2 in 3 patients, 500 mg/m2 in 5 patients, 600 mg/m2 in 6 patients, and 700 mg/m2 in 2 patients, demonstrating significant differences among individual patients. Grade 3 marrow depression occurred in only 1 patient (5.6%). Of these 18 patients, 3 (16.7%), 13 (72.2%) and 2 (11.1%) patients showed partial response, stable disease, and progressive disease, respectively. The median of times to progressive disease and survival were 4.5 and 9.5 months, respectively. There were no significant differences in 1-year survival time and more than 50% reduction rate of serum CA19-9, a tumor marker for pancreatic cancer, between patients with lower (500 mg/m2 or less) and higher (600 mg/m2 or more) iMRD. CONCLUSION: These results suggest that iMRD is a simple method to determine an individual's tailored dose for chemotherapy and could be the optimal dose for patients with noncurable cancers such as metastatic pancreas cancer.

Takamatsu, S., D. Ban, et al. (2005). "Resection of a cancer developing in the remnant pancreas after a pancreaticoduodenectomy for pancreas head cancer." J Gastrointest Surg **9**(2): 263-9.

We report a rare case of a curative resection performed on a carcinoma developing in the remnant pancreas at 3 years 7 months after a pancreaticoduodenectomy for pancreatic cancer. A 63-year-old man underwent a pancreaticoduodenectomy for pancreatic cancer on November 1999. Because the celiac trunk was occluded by atherosclerosis, an aortohepatic bypass with a saphenous vein graft was performed simultaneously. In May 2003, tumor marker levels increased, and a tumor was detected in the remnant pancreas on computed tomography. There were no findings such as invasion into the surrounding tissue or distant metastasis, and therefore we removed the remnant pancreas in July 2003. Histopathologically, the tumor consisted of a well-differentiated tubular adenocarcinoma and was limited to the pancreas. Moreover, the anastomotic site of the pancreaticojejunostomy was negative for cancer, and some foci of papillary hyperplasia and goblet cell metaplasia of the pancreatic ductal epithelium, which was thought to be the precursor of the pancreatic cancer, were seen. These findings suggested that the tumor was a second primary cancer developing in the remnant pancreas. This case provided suggestive evidence for the development of pancreatic cancer, and the surgical procedure for a pancreaticoduodenectomy with occlusion of the celiac trunk is discussed.

Talamonti, M. S., P. J. Catalano, et al. (2000). "Eastern Cooperative Oncology Group Phase I trial of protracted venous infusion fluorouracil plus weekly gemcitabine with concurrent radiation therapy in patients with locally advanced pancreas cancer: a

regimen with unexpected early toxicity." J Clin Oncol **18**(19): 3384-9.

PURPOSE: We performed a phase I trial of protracted venous infusion (PVI) fluorouracil (5-FU) plus weekly gemcitabine with concurrent radiation therapy in patients with locally advanced pancreas cancer to determine the maximum-tolerated dose of gemcitabine that could be safely administered. We also sought to identify the toxicities associated with this treatment protocol. PATIENTS AND METHODS: Seven patients with locally advanced pancreas cancer were treated with planned doses of radiation (59.4 Gy) and PVI of 5-FU (200 mg/m(2)/d) with gemcitabine doses of 50 to 100 mg/m(2)/wk. RESULTS: Two of three patients at the 100-mg/m(2)/wk dose level experienced dose-limiting toxicity (DLT), as did three of four at the 50-mg/m(2)/wk dose level. One patient experienced a mucocutaneous reaction described as a Stevens-Johnson syndrome that was attributed to chemotherapy. Three patients developed gastric or duodenal ulcers with severe bleeding requiring transfusion. One patient developed severe thrombocytopenia lasting longer than 4 weeks. Three of the five episodes of DLT developed at radiation doses < or = 36 Gy. CONCLUSION: Based on this experience, we cannot recommend further investigation of regimens incorporating gemcitabine into regimens of radiation with PVI 5-FU. The mechanism of this synergistic toxicity remains to be determined.

Tamura, K., S. Sumi, et al. (1997). "A splenic-inferior mesenteric venous anastomosis prevents gastric congestion following pylorus preserving pancreatoduodenectomy with extensive portal vein resection for cancer of the head of the pancreas." Int Surg **82**(2): 155-9.

BACKGROUND: In order to prevent gastric congestion after both of the splenic and coronary veins were taken as part of extensive portal vein resection in pylorus preserving (PP) pancreatoduodenectomy (PD), we made a splenic-inferior mesenteric venous (SpIMV) anastomosis. MATERIALS AND METHODS: Four patients underwent PP subtotal PD with such extensive portal vein resection under the diagnosis of pancreas head cancer. The portal vein was reconstructed by end-to-end anastomosis, and the coronary vein was ligated. Since the stump of the splenic vein could not be approximated to the portal or superior mesenteric vein, shunting the splenic venous flow to the inferior mesenteric vein was attempted by making a SpIMV anastomosis in 3 patients and by preserving the SpIMV confluence in a patient. Postoperative celiac angiography showed that venous outflow from the stomach, spleen and remnant pancreas collected into the splenic vein and passed through the SpIMV anastomosis or confluence, and finally drained into the portal vein by inferior mesenteric to superior mesenteric collateral. RESULTS: No remarkable congestion of the stomach was observed. CONCLUSIONS: In conclusion making a SpIMV anastomosis or preserving the SKpIMV confluence is beneficial for preventing gastric congestion following PP PD with extensive portal vein resection for cancer of the head of the pancreas.

Tan, T. S. and A. Jatoi (2008). "An update on advance directives in the medical record: findings from 1186 consecutive patients with unresectable exocrine pancreas cancer." J Gastrointest Cancer **39**(1-4): 100-3.

BACKGROUND: The Terri Schiavo case and other recent events underscore the importance of advance directives. Yet, in the past, only a small subgroup has utilized them. This study from a large tertiary medical center was undertaken to assess current rates of advance directives among patients with incurable pancreas cancer. METHODS/RESULTS: The medical records of 1,186 consecutive patients with unresectable pancreas cancer were reviewed over a 4-year span. Only 174 patients (15%) had an advance directive in the medical record. Older age and having cancer therapy at our institution were associated with a greater likelihood of having an advance directive with odds ratios (95% confidence intervals) of 8.26 (2.81, 24.93) and 2.86 (2.03, 4.02), respectively, in multivariate analyses. Importantly, 42 patients (24%) had a different person designated as their healthcare agent in their advanced directive than what appeared in the medical record as the "contact person." CONCLUSION: These findings underscore the ongoing need to discuss advance directives with patients with incurable malignancies and to clarify patients' wishes when seemingly contradictory information appears in other parts of the medical record.

Tohnosu, N., K. Narushima, et al. (2006). "A case of breast cancer metastatic to the tail of the pancreas." Breast Cancer **13**(2): 225-9.

Breast cancer metastasis to pancreas is rarely seen. There have been only 6 cases described in the literature. We present the seventh case of a 54-year-old woman with breast cancer that metastasized to the tail of the pancreas 4 years and 4 months after radical mastectomy. Although the serum levels of CA15-3 and TPA had gradually increased without symptoms, it was difficult to establish the diagnosis before contrast-enhanced abdominal CT scan was performed. Immunohistochemical staining using E-cadherin was

positive, proving that the breast cancer was ductal rather than lobular in origin. CA15-3 immunohistochemically stained positive in the resected pancreas lesion. Positive monoclonal staining by GCDFP-15 (gross cystic disease fluid protein-15) in the pancreas tumor also confirmed it breast cancer origin. Investigation of chemokine/chemokine receptors may clarify a new mechanism of metastasis to the pancreas from breast cancer.

Tomlinson, J. S., S. Jain, et al. (2007). "Accuracy of staging node-negative pancreas cancer: a potential quality measure." Arch Surg **142**(8): 767-723; discussion 773-4.

OBJECTIVE: To determine the optimal number of lymph nodes to examine for accurate staging of node-negative pancreatic adenocarcinoma after pancreaticoduodenectomy. DESIGN, SETTING, AND PATIENTS: Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (1988-2002) were used to identify 3505 patients who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreas, including 1150 patients who were pathologically node negative (pN0) and 584 patients with a single positive node (pN1a). Perioperative deaths were excluded. Univariate and multivariate survival analyses were performed. MAIN OUTCOME MEASURE: Examination of 15 lymph nodes appears to be optimal for accurate staging of node-negative adenocarcinoma of the pancreas after pancreaticoduodenectomy. RESULTS: The number of nodes examined ranged from 1 to 54 (median, 7 examined nodes). Univariate survival analysis demonstrated that dichotomizing the pN0 cohort on 15 or more examined lymph nodes resulted in the most statistically significant survival difference (log-rank chi(2) = 14.49). Kaplan-Meier survival curves demonstrated a median survival difference of 8 months ($P < .001$) in favor of the patients who had 15 or more examined nodes compared with patients with fewer than 15 examined nodes. Multivariate analysis validated that having 15 or more examined nodes was a statistically significant predictor of survival (hazard ratio, 0.63; 95% confidence interval, 0.49-0.80; $P < .0001$). Furthermore, a multivariate model based on the survival benefit of each additional node evaluated in the pN0 cohort demonstrated only a marginal survival benefit for analysis of more than 15 nodes. Approximately 90% of the pN1a cohort was identified with examination of 15 nodes. CONCLUSIONS: Examination of 15 lymph nodes appears to be optimal to accurately stage node-negative adenocarcinoma of the pancreas after pancreaticoduodenectomy. Furthermore, evaluation of at least 15 lymph nodes of a pancreaticoduodenectomy specimen may serve as a quality measure in the treatment of pancreatic adenocarcinoma.

Torres, M. J., F. Ruiz-Cabello, et al. (1996). "Loss of an HLA haplotype in pancreas cancer tissue and its corresponding tumor derived cell line." Tissue Antigens **47**(5): 372-81.

A combination of immunohistochemical, biochemical, and recombinant DNA techniques were used to investigate class I expression in 26 pancreatic adenocarcinomas and 6 autologous tumor-derived cells. The prevalence of HLA losses was found to be comparable to that observed in other tumor types (> 35%), using monomorphic and locus-specific antibodies. In one patient, the original tumor tissue, a tumor derived cell line (IMIM-PC-2), and EBV-transformed lymphocytes were available for study. The patient's phenotype was A25, A30, B18, B18. However, A30 allele product could not be detected in the original tumor not in the cultured tumor cells. In addition, A30 allele could not be isolated from cDNA or genomic clones from the cultured tumor cells whereas it was isolated from the autologous lymphoblastoid cell line. Using isoelectric focusing analysis a significant reduction in the B18 heavy chain product was also observed in the tumor cell line, IMIM-PC-2, suggesting the absence of expression of one allele. Further studies revealed loss of heterozygosity at DR and other loci of chromosome 6 and cytogenetic data strongly suggested deletion of a full chromosome 6. This work indicates for the first time that loss of a full HLA haplotype occurs in tumor tissue and suggests that this mechanism may contribute to the progression of human cancer.

Ulrich, A. B., B. M. Schmied, et al. (2002). "Differences in the expression of glutathione S-transferases in normal pancreas, chronic pancreatitis, secondary chronic pancreatitis, and pancreatic cancer." Pancreas **24**(3): 291-7.

INTRODUCTION: In our previous study, glutathione S-transferase-pi (GST-pi), a phase II drug metabolizing enzyme, was found to be expressed in pancreatic ductal and ductular cells but not acinar cells of the normal pancreas, chronic pancreatitis, and secondary pancreatitis caused by pancreatic cancer. A greater percentage of the cells expressing GST-pi was shown in the islets of chronic pancreatitis specimens compared with the normal pancreas and secondary pancreatitis. AIMS AND METHODOLOGY: To examine whether the increased number of islet cells expressing GST-pi and the absence in the acinar cells are compensated for by other GST isozymes, we investigated the expression of GST-alpha and GST-mu in the same specimens. RESULTS: Unlike the distribution of GST-pi, the distribution of GST-alpha

and GST-mu in islets did not show marked differences between the three groups. However, in four of 18 primary chronic pancreatitis specimens, more islet cells (approximately 25%) expressed GST-alpha than in the normal pancreas and secondary chronic pancreatitis (both approximately 10%). The reactivity of cancer cells to GST-alpha, GST-mu, and GST-pi was similar to the ductal cells in the normal pancreas, chronic pancreatitis, and secondary chronic pancreatitis. Contrary to the expression of GST-pi, no statistically significant differences were found in the distribution of GST-alpha and GST-mu in the normal pancreas, chronic pancreatitis, and secondary chronic pancreatitis. CONCLUSION: The expression of the other GSTs does not compensate for the variation of expression of GST-pi. There was no specimen in each group that did not express at least one GST isozyme in islet, acinar, and ductal cells.

Urbach, D. R., L. L. Swanstrom, et al. (2001). "Incidence of cancer of the pancreas, extrahepatic bile duct and ampulla of Vater in the United States, before and after the introduction of laparoscopic cholecystectomy." Am J Surg **181**(6): 526-8.

BACKGROUND: Some epidemiologic studies have identified cholecystectomy as a risk factor for pancreatic and biliary cancer. METHODS: We compared the incidence of cancers of the pancreas, extrahepatic bile duct and ampulla of Vater before and after the widespread adoption of laparoscopic cholecystectomy in the United States in 1991, when the use of cholecystectomy increased dramatically. RESULTS: Compared with 1980 to 1991, there was no increase in the incidence of cancer of the pancreas (adjusted incidence rate ratio [IRR] 0.97, 95% confidence interval [CI] 0.94 to 0.99) or extrahepatic bile duct (IRR 0.80, 95% CI 0.74 to 0.87) during 1992 to 1996. There was a small increase in the incidence of ampullary cancer (IRR 1.14, 95% CI 1.03 to 1.26). CONCLUSIONS: We did not find clear evidence of a short-term increase in the incidence of cancers of the pancreas, bile duct, and ampulla of Vater, that was attributable to the increased use of cholecystectomy.

Valean, S., P. Armean, et al. (2008). "Cancer mortality in Romania, 1955-2004. Digestive sites: esophagus, stomach, colon and rectum, pancreas, liver, gallbladder and biliary tree." J Gastrointestin Liver Dis **17**(1): 9-14.

AIM: Until recently, gastric cancer was the most frequent digestive neoplasia in our country. Our study presents the first synthesis of data regarding mortality rates from digestive cancers, for a period covering 50 years, in Romania. METHODS: Age-standardized mortality rates /100,000 population, general and/or per gender, concerning six digestive cancers, were identified from the statistics of IARC/OMS (Lyon, France) (years 1955-2002) and of the Ministry of Public Health (Bucharest, Romania) (year 2004). For 2002, incidence and mortality rates per sex from digestive cancers were available and case fatality ratios could be calculated as an approximation of survival rates, as well as sex ratio. RESULTS: Age standardized mortality rates per sex and cancer site registered the following changes: esophageal cancer increased from 2.03/0.62 (M/F) to 2.8/0.5; gastric cancer registered a decrease, from 33.14/18.77 to 17.0/6.6; colorectal cancer increased from 4.65/4.57 to 13.6/9.0; pancreatic cancer increased from 5.50/2.92 to 8.1/4.2 and liver cancer (including peripheric cholangiocarcinoma) increased from 1.77/0.83 to 8.8/3.9. In our population, the case fatality ratio appeared to be better only in colorectal cancer, 0.61 in males and 0.62 in females, respectively. Sex ratio was highest for esophageal cancer (males/females 5.8/1) and lowest for colorectal cancer (1.5/1). CONCLUSIONS: Our study found opposite trends in the mortality rates from digestive cancers, with gastric cancer rates decreasing and the other five digestive cancers increasing. A new hierarchy of digestive cancers has been drawn up, with colorectal cancer as the main cause of death, and gastric cancer in second position, followed by pancreatic, liver, esophageal, and gallbladder and biliary tree cancers.

Viehl, C. T., T. T. Moore, et al. (2006). "Depletion of CD4+CD25+ regulatory T cells promotes a tumor-specific immune response in pancreas cancer-bearing mice." Ann Surg Oncol **13**(9): 1252-8.

BACKGROUND: Pancreas cancer-bearing mice have an increased prevalence of immunosuppressive CD4(+)CD25(+) regulatory T cells (T(reg)). Depletion of T(reg) results in smaller tumors and prolonged host survival. The objective of this study was to evaluate the tumor-specific immune response after depletion of T(reg) alone or in combination with a cancer vaccine. METHODS: Four groups of C57BL/6 mice were challenged with pancreas adenocarcinoma cells (Pan02). The mice received four combinations of antibody-mediated T(reg) depletion and whole tumor cell vaccination: (1) no treatment, (2) T(reg) depletion only, (3) vaccination only, or (4) T(reg) depletion and vaccination. Splenocytes and lymphocytes from tumor-draining lymph nodes were analyzed for tumor-specific release of interferon gamma by enzyme-linked immunosorbent spot assay. RESULTS: In T(reg)-depleted and vaccinated mice, a strong statistical trend toward smaller tumors (P = .05) and longer survival (P = .054) was found compared with untreated mice. T(reg)-depleted mice showed

significantly more tumor-specific cells than undepleted mice (P = .02). The number of tumor-specific cells was significantly higher in tumor-draining lymph nodes than in the spleen (P = .002). Similarly, significantly more tumor-specific cells were found in spleens of T(reg)-depleted and vaccinated mice than in vaccinated-only mice (P = .009). CONCLUSIONS: Depletion of T(reg) alone or in combination with a whole tumor cell vaccine promotes a tumor-specific immune response. Thus, strategies incorporating T(reg) depletion might improve the efficacy of cancer vaccines.

Virlos, I. T., H. P. Siriwardana, et al. (2005). "Pathways of care for patients with suspected cancer of the pancreas: a tiered questionnaire-based survey of medical personnel across a single United kingdom Calman-Hine cancer network." Jop **6**(1): 13-25.

OBJECTIVE: This study examines clinical management pathways for patients with suspected pancreatic cancer within a single United Kingdom Calman-Hine NHS cancer network with particular focus on referral patterns and the primary care-hospital specialist interface. METHODS: A questionnaire-based study appraising responses from three key groups (general practitioners, gastrointestinal physicians and gastrointestinal surgeons) practising within a cancer network. The questionnaire addressed caseload, referral pathways, multidisciplinary care teams and involvement of specialists. PARTICIPANTS: The study population comprised 448 general practitioners, 14 gastroenterologists and 23 gastrointestinal surgeons. RESULTS: The mean number of new patients with suspected pancreatic cancer seen per general practitioner per annum was 0.4 (range: 0-1). Fifty-three percent of general practitioners refer to gastrointestinal physicians and 47% to gastrointestinal surgeons. In hospital, a relatively large number of physicians and surgeons see a small number of new patients each per annum. The involvement of multidisciplinary teams and referral of patients with non-resectable disease for chemotherapy is limited. Fourteen (60.9% out of 23 general surgeons) refer all patients to pancreatic specialists, 4 (17.4%) selectively refer and 5 (21.7%) never refer. CONCLUSION: The findings suggest divergence in standards of care from those advocated in governmental cancer strategic plans. In particular, not all patients with suspected pancreatic cancer see specialists, many hospital specialists see small numbers of cases and multidisciplinary care is limited.

Wachtel, M. S., K. T. Xu, et al. (2008). "Pancreas cancer survival in the gemcitabine era." Clin Med Oncol **2**: 405-13.

After multiple positive studies, gemcitabine, approved for the treatment of pancreas cancer by the FDA in 1977, became standard of care. Whether this therapeutic advance has translated into longer survival for pancreas cancer patients in general has not been established. This study, derived from SEER (Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute) data, compared the survival experiences of the gemcitabine (1998-2004) and pre-gemcitabine (1988-1997) eras for 7,151 patients who had metastatic disease and did not undergo extirpative surgery, 14,369 patients who had not undergone surgery and had metastases, 5,042 patients who had undergone surgery and did not have metastases, and 5,011 patients who had undergone surgery and had metastases. Calculated survival time ratios (TR) were adjusted for radiotherapy history, grade, nodal status, loco-regional extent of disease, age, race, and gender. For those who did not undergo extirpative surgery, improvements in survival in the gemcitabine era (1998-2004) versus the prior time period (1988-1997) seen for patients with metastatic cancer (TR = 1.20, 95% c.i. 1.15-1.25) were not seen for those without metastatic cancer (TR = 1.05, 95% c.i. 1.00-1.15). For those who did undergo extirpative surgery, improvements were much more dramatic for those with metastatic cancer (TR = 1.61, 95% c.i. 1.45-1.80) than those without metastases (TR = 1.23, 95% c.i. 1.15-1.31). The results are consistent with the notion that the promising findings with respect to gemcitabine in the controlled clinical trials have found expression in the general population of patients with pancreas cancer.

Wahid, N. A., A. I. Neugut, et al. (1996). "Response of small cell carcinoma of pancreas to a small cell lung cancer regimen: a case report." Cancer Invest **14**(4): 335-9.

Small cell carcinoma of the pancreas is a very rare malignancy with 18 cases reported in the literature, of which only 3 were treated with chemotherapy. A 52-year-old man was diagnosed with small cell carcinoma originating in the head of the pancreas and invading the duodenum. He was treated with a similar approach as for localized small cell lung cancer, with six cycles of combination chemotherapy and local radiotherapy, and went into complete remission. After 3 months, he developed liver metastases along with an enlarged left supraclavicular lymph node. He was treated with two cycles of CVA, but developed lung metastases and was treated with ifosfamide/mesna. However, his overall condition deteriorated and hospice care was instituted until the patient's demise. The patient survived 14 months following diagnosis, significantly longer than the 15 reported patients with small cell pancreatic

carcinomas not treated with chemotherapy. Combination chemotherapy and radiation therapy as it is utilized for small cell lung cancer appear to be beneficial for small cell carcinoma of the pancreas.

Wente, M. N., J. Kleeff, et al. (2005). "Renal cancer cell metastasis into the pancreas: a single-center experience and overview of the literature." Pancreas **30**(3): 218-22.

OBJECTIVES: The pancreas is a rare target for metastasis from other primary cancers, but pancreatic metastasis play a role in the diagnostic workup of patients with pancreatic tumors, especially in patients with a history of renal cell carcinoma (RCC). METHODS: Between October 2001 and June 2004 data from 601 patients undergoing pancreatic resection were entered prospectively in a database and were analyzed for metastasis into the pancreas from RCC. RESULTS: Fifteen patients with metastasis to the pancreas from RCC were identified. One patient showed metastatic disease at time of primary diagnosis. In 8 patients, the pancreas was the only site of metastasis, whereas in 7 patients, other organs, such as the thyroid gland, the lung, or the liver, were targets of metastasis, either metachronous or simultaneous at the time of pancreatic metastasis. The median interval between primary treatment of RCC and occurrence of pancreatic metastasis was 86 months (range, 0-258). Most patients were asymptomatic and diagnosed during standard tumor follow-up. So far, 14 patients remain alive with a median follow-up of 10 months. CONCLUSION: Pancreatic metastasis from RCC is rare but can occur even more than 20 years after primary tumor manifestation. Our results show that pancreatic resections for metastasis can be performed safely with a low rate of complications. Patients with a history of RCC should undergo a long-term follow-up to detect and evaluate for pancreatic metastases as well for metastasis to other organ sites.

Whitehead, R. P., S. McCoy, et al. (2006). "A Phase II trial of epothilone B analogue BMS-247550 (NSC #710428) ixabepilone, in patients with advanced pancreas cancer: a Southwest Oncology Group study." Invest New Drugs **24**(6): 515-20.

PURPOSE: The purpose of this Phase II multi-institutional study was to define the efficacy and toxicity of ixabepilone in patients with advance pancreatic adenocarcinoma. PATIENTS AND METHODS: Patients were required to have pancreatic adenocarcinoma and metastatic or recurrent disease that was not amenable to curative resection. Performance status was 0-1, and patients could not have had prior chemotherapy, or chemoradiation therapy for their advanced disease although prior local palliative radiation was allowed. Ixabepilone was administered iv as a 3 hour infusion every 21 days. Initially, the dose was 50 mg/m(2) but this was lowered to 40 mg/m(2) shortly after the trial opened because of concerns about neurotoxicity. RESULTS: Sixty-two patients were registered however 2 were ineligible because they did not have recurrent or metastatic disease. For the 60 eligible patients, 22 had performance status of 0 and 38 performance status of 1. The estimated 6-month survival was 60% (95% CI 48%-72%) with a median survival of 7.2 months and an estimated time to treatment failure of 2.3 months. Out of 56 patients with measurable disease there were 5 confirmed partial responses for a confirmed response probability of 9% (95% CI 3%-20%) and 7 unconfirmed partial responses for an overall response probability of 21% (95% CI 12%-34%). Common toxicities were neutropenia/granulocytopenia, nausea and vomiting and neuropathy. There was one death, cause not determined but judged "possibly" related to treatment. CONCLUSION: Ixabepilone shows encouraging activity in patients with advanced pancreatic cancer and should be investigated further in this disease.

Wilentz, R. E. and R. H. Hruban (1998). "Pathology of cancer of the pancreas." Surg Oncol Clin N Am **7**(1): 43-65.

Although many have lumped nearly 20 different neoplasms under the umbrella term "cancer of the pancreas," each of these neoplasms is pathologically and clinically distinct. In addition, each may require a specific treatment and result in a different outcome. Understanding the pathology of pancreas cancer, therefore, forms the cornerstone for rational treatment and prognostication. This article describes the pathology of a number of primary, metastatic, and systemic cancers that can involve the pancreas. The clinical relevance of each gross and histologic tumor feature is emphasized.

Wilson, R. L., R. K. Brown, et al. (2009). "Surgical resection for metastatic non-small cell lung cancer to the pancreas." Lung Cancer **63**(3): 433-5.

We report the case of a woman with non-small cell lung cancer (NSCLC) metastatic to the pancreas who underwent pancreatic resection followed by a significant disease-free interval. Resection of NSCLC metastases, other than those to the brain and adrenal gland, are rarely reported. We could not identify any other cases of pancreatic metastasis resection in the literature. This case proves, in principle, that resection of solitary metastatic lesions in certain clinical conditions can be improved regardless of location.

Yamagishi, F., H. Arai, et al. (2004). "Partial separating gastrojejunostomy for incurable cancer of the stomach or pancreas." Hepatogastroenterology **51**(60): 1623-5.

BACKGROUND/AIMS: Advanced stomach or pancreas cancer with antral obstruction has been treated by gastrojejunostomy. The delayed return of gastric emptying, however, frequently occurs. The Devine exclusion procedure has been reported to be the better bypass operation in terms of oral intake, but it needs a drainage tube. In cases where the lesser curvature is invaded, this operation should be avoided. A method of gastroenterostomy, which is safe and shows good outcomes concerning oral intake, is desired. METHODOLOGY: Among 15 patients with advanced stomach or pancreas cancer, 8 received conventional gastrojejunostomy (CG Group), 3 Devine exclusive gastrectomy with a drainage tube (DE Group) and 4 partial separating gastrojejunostomy (PG Group). The partial separating gastrojejunostomy was performed as follows. The stomach was partially partitioned using GIA from the side of the greater curvature. The posterior side of the proximal stomach was anastomosed with the proximal jejunum using a circular stapler instrument. RESULTS: All patients in the DE and SG Groups could eat regular or semi-regular meals. The bleeding from tumor in the DE Group was less than that in the SG and CG Groups. CONCLUSIONS: In cases where the lesser curvature is invaded by tumor or lymph node metastasis, partial separating gastrojejunostomy would be recommended as a substitute for the Devine procedure.

Yamaguchi, T., M. Miyata, et al. (1997). "Histometric analysis of the distal pancreas in pancreatic head cancer." Surg Today **27**(5): 420-8.

To clarify the histological status of the pancreas tail after pancreatoduodenectomy (PD), fibrosis, islets of Langerhans, and A, B, and D cells were examined histometrically in surgical cases of pancreatic cancer. The same investigations were also performed during an autopsy examination of the pancreas tail of survivors of surgery who had received either PD or total pancreatectomy with segmental autotransplantation (SAT). In the surgical cases, fibrosis and the islet percentage compared with nonpancreatic cancer cases were significantly higher while the B cell ratio was significantly lower. In addition, in pancreatic cancer patients, the fibrosis and islet ratio in the group with a blocked pancreatic duct were higher while the B cell ratio was lower than in the group with an open pancreatic duct. A direct relationship between the islet ratio and the degree of fibrosis, and an inverse relationship between the B cell ratio and the degree of fibrosis, were thus found. From the autopsy cases, the fibrosis progressed and the islet ratio increased following PD, but after SAT only the islet ratio increased compared to the time of surgery. The progression of fibrosis after PD thus suggests the presence of some problems in both the surgical method and postoperative management.

Yang, L., R. Hwang, et al. (1996). "Gene therapy of metastatic pancreas cancer with intraperitoneal injections of concentrated retroviral herpes simplex thymidine kinase vector supernatant and ganciclovir." Ann Surg **224**(3): 405-14; discussion 414-7.

OBJECTIVE: The objective of this study was to determine the efficacy of intraperitoneal (IP) injections of a new concentrated herpes simplex thymidine kinase (HS-tk) retroviral vector and ganciclovir (GCV) for peritoneal metastases from pancreas cancer. SUMMARY BACKGROUND DATA: Metastatic pancreas cancer is fatal. Gene therapy may provide a novel approach for this disease. Gene therapy with adeno- or retroviral-mediated transfer of the HS-tk gene into tumor cells renders the cells susceptible to GCV. Intratumoral or intracavity injections of retroviral vectors have been ineffective in previous studies. METHODS: Pancreatic cancer B x PC3 cells (3 x 10(7)) were injected into the tail of pancreas in nude mice. Mice received IP injections of a concentrated HS-tk vector (5 x 10(7)) cfu/mliters) or a control vector (G1Na) without the tk gene for 10 days and GCV (100 mg/kg) for 14 days. To determine whether the vector would survive in the milieu of the peritoneal cavity, the authors examined the effects of ascitic fluid on the vector. Pancreas cancer cells were transduced in vitro with HS-tk vector in presence of media or ascitic fluid and treated with GCV. RESULTS: Highly significant reductions in the mass of metastatic peritoneal tumor deposits were found in HS-tk-treated group (124 +/- 27 mg; n = 11) compared with G1Na vector controls (910 +/- 168 mg; n = 8; $p < 0.0001$). Results of polymerase chain reaction analysis demonstrated integration of the vector in the tumors, and on immunohistochemistry, expression of the TK protein was seen in the number of surviving colonies (representing nontransduced cells) were similar in both groups, suggesting that the vector effectively transduced tumor cells bathed in the ascitic fluid. CONCLUSIONS: Results demonstrate that IP administration of concentrated retroviral HS-tk vectors is effective treatment for pancreas cancer metastatic to the peritoneal cavity; furthermore, the vector is active in the presence of ascitic fluid. Intraperitoneal retroviral HS-tk may provide a novel approach to treatment of metastatic pancreas cancer.

Yantiss, R. K., B. A. Woda, et al. (2005). "KOC (K homology domain containing protein overexpressed in

cancer): a novel molecular marker that distinguishes between benign and malignant lesions of the pancreas." Am J Surg Pathol **29**(2): 188-95.

KOC (K homology domain containing protein overexpressed in cancer) is a novel oncofetal RNA-binding protein highly expressed in pancreatic carcinomas. Recently, Corixa Corporation developed a monoclonal antibody specific for KOC that can be used with standard immunohistochemical techniques. The purposes of this study were 1) to assess KOC mRNA expression in pancreatic carcinoma, 2) to determine the pattern of KOC immunoexpression among benign, borderline, and malignant pancreatic epithelial lesions, and 3) to evaluate the utility of the KOC antibody in distinguishing between these entities. mRNA was isolated from fresh pancreatic tissues (19 carcinomas, 2 normal pancreas, 1 chronic pancreatitis) and amplified using standard RT-PCR techniques. Fifteen of 19 (79%) carcinomas overexpressed KOC mRNA relative to non-neoplastic tissue samples and expression increased progressively with tumor stage: the mean copy number of KOC mRNA transcripts was 1.5, 11.1, 31, and 28 for stage I, II, III, and IV carcinomas, respectively, compared with 0.9 and 1 for normal pancreatic tissue and chronic pancreatitis, respectively. Immunostains using the KOC antibody were performed on 50 surgical resection specimens (38 invasive adenocarcinomas, 3 intraductal papillary-mucinous neoplasms, 2 mucinous cystic neoplasms, 7 chronic pancreatitis). KOC staining was present in 37 of 38 (97%) carcinomas: the staining reaction was moderate or strong in 36 of 38 (94%) and present in >50% of the tumor cells in 35 of 38 (92%) cases. Severe dysplasia of the ductal epithelium, present in 19 foci of intraductal papillary mucinous carcinoma, mucinous cystadenocarcinoma, and grade 3 pancreatic intraepithelial neoplasia (PanIN3) showed strong or moderate staining in 15 (79%) cases, whereas foci of mild and moderate dysplasia (intraductal papillary-mucinous neoplasms and mucinous cystic neoplasms with adenoma and/or moderate dysplasia, PanIN1, and PanIN2) were uniformly negative for this marker in 25 and 22 cases, respectively. In the normal pancreas, weak background staining of acini was present in 12 of 50 (24%) cases but was easily distinguishable from the type of staining identified in neoplastic epithelium, and benign ducts and ductules were negative in all cases. Four of 38 (11%) foci of chronic pancreatitis, present in the 7 resections performed for chronic pancreatitis as well as 31 foci of peritumoral chronic pancreatitis, showed weak staining in <10% of the ductules. We conclude that KOC is a sensitive and specific marker for carcinomas and high-grade dysplastic lesions of the pancreatic ductal epithelium. Therefore, immunostains directed against KOC may be of diagnostic utility in the evaluation of pancreatic lesions, particularly when biopsy material is limited.

Yeo, C. J., J. L. Cameron, et al. (1995). "Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients." Ann Surg **221**(6): 721-31; discussion 731-3.

OBJECTIVE: This single-institution study examined the outcome after pancreaticoduodenectomy in patients with adenocarcinoma of the head of the pancreas. SUMMARY OF BACKGROUND DATA: In recent years, pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas has been associated with decreased morbidity and mortality and, in some centers, 5-year survival rates in excess of 20%. METHODS: Two hundred one patients with pathologically verified adenocarcinoma of the head of the pancreas undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital between 1970 and 1994 were analyzed (the last 100 resections were performed between March 1991 and April 1994). This is the largest single-institution experience reported to date. RESULTS: The overall postoperative in-hospital mortality rate was 5%, but has been 0.7% for the last 149 patients. The actuarial 5-year survival for all 201 patients was 21%, with a median survival of 15.5 months. There were 11 5-year survivors. Patients resected with negative margins (curative resections: n = 143) had an actuarial 5-year survival rate of 26%, with a median survival of 18 months, whereas those with positive margins (palliative resections; n = 58) fared significantly worse, with an actuarial 5-year survival rate of 8% and a median survival of 10 months ($p < 0.0001$). Survival has improved significantly from decade to decade ($p < 0.002$), with the 3-year actuarial survival of 14% in the 1970s, 21% in the 1980s, and 36% in the 1990s. Factors significantly favoring long-term survival by univariate analyses included tumor diameter < 3 cm, negative nodal status, diploid tumor DNA content, tumor S phase fraction < 18%, pylorus-preserving resection, < 800 mL intraoperative blood loss, < 2 units of blood transfused, negative resection margins, and use of postoperative adjuvant chemotherapy and radiation therapy. Multivariate analyses indicated the strongest predictors of long-term survival were diploid tumor DNA content, tumor diameter < 3 cm, negative nodal status, negative resection margins, and decade of resection. CONCLUSIONS: The survival of patients with pancreatic adenocarcinoma treated by pancreaticoduodenectomy is improving. Aspects of tumor biology, such as DNA content, tumor diameter, nodal status and margin status, are the strongest predictors of outcome.

Yermilov, I., D. Bentrem, et al. (2009). "Readmissions following pancreaticoduodenectomy for pancreas cancer: a population-based appraisal." Ann Surg Oncol **16**(3): 554-61.

Procedure complexity and volume-outcome relationships have led to increased regionalization of pancreaticoduodenectomy (PD) for pancreas cancer. Knowledge regarding outcomes after PD comes from single-institutional series, which may be limited if a significant number of patients follow up at other hospitals. Thus, readmission data may be underreported. This study utilizes a population-based data set to examine readmission data following PD. California Cancer Registry (1994-2003) was linked to the California's Office of Statewide Health Planning and Development (OSHPD) database; patients with pancreatic adenocarcinoma who had undergone PD, excluding perioperative (30-day) mortality, were identified. All hospital readmissions within 1 year following PD were analyzed with respect to timing, location, and reason for readmission. Our cohort included 2,023 patients who underwent PD for pancreas cancer. Fifty-nine percent were readmitted within 1 year following PD and 47% were readmitted to a secondary hospital. Readmission was associated with worse median survival compared with those not readmitted (10.5 versus 22 months, $p<0.0001$). Multivariate analysis revealed that increasing T-stage, age, and comorbidities were associated with increased likelihood of readmission. Diagnoses associated with high rates of readmission included progression of disease (24%), surgery-related complications (14%), and infection (13%). Diabetes (1.4%) and pain (1.5%) were associated with low rates of readmission. We found a readmission rate of 59%, which is much higher than previously reported by single institutional series. Concordantly, nearly half of patients readmitted were readmitted to a secondary hospital. Common reasons for readmission included progression of disease, surgical complications, and infection. These findings should assist in both anticipating and facilitating postoperative care as well as managing patient expectations. This study utilizes a novel population-based database to evaluate incidence, timing, location, and reasons for readmission within 1 year following pancreaticoduodenectomy. Fifty-nine percent of patients were readmitted within 1 year after pancreaticoduodenectomy and 47% were readmitted to a secondary hospital.

Yi, S. Q., K. Miwa, et al. (2003). "Innervation of the pancreas from the perspective of perineural invasion of pancreatic cancer." Pancreas **27**(3): 225-9.

INTRODUCTION: Pancreatic cancer invasion via neural routes (perineural invasion) has been studied extensively, but detailed research on the morphology of innervation of the pancreas related to perineural invasion is scarce. AIMS: To clarify the morphology of neural distribution in the human pancreas. METHODOLOGY: The pancreas and surrounding structures were dissected in 9 cadavers, the specimens were immersed in a 0.001% solution of alizarin red S in ethanol to stain the peripheral nerves, and the detailed distribution was studied to confirm the extrapancreatic and intrapancreatic plexus using a binocular microscope. RESULTS: The innervation of the uncinate process of the pancreas originated from the superior mesenteric plexus (SMPlx) along the inferior pancreaticoduodenal artery (IPDA), but did not form a wide offshoot of nerve bundles as reported. Concerning the innervation of the body and tail, it was found that the nerve fibers entered the pancreas immediately after leaving the celiac plexus, and were distributed around the pancreatic duct in a twig-like manner. CONCLUSION: It was emphasized that the nerve originating from SMPlx to the uncinate process chiefly ran along the IPDA and it was necessary to focus one's attention not only on the extrapancreatic perineural invasion but also on the intrapancreatic perineural invasion in carcinoma of the body and tail of the pancreas.

Yilmaz, G., K. Aydin, et al. (2006). "Post-ERCP bacteremia caused by Alcaligenes xylosoxidans in a patient with pancreas cancer." Ann Clin Microbiol Antimicrob **5**: 19.

Alcaligenes xylosoxidans is an aerobic, motile, oxidase and catalase positive, nonfermentative Gram negative bacillus. This bacterium has been isolated from intestine of humans and from various hospital or environmental water sources. A.xylosoxidans is both waterborne and results from the poor-hygienic conditions healthcare workers are in. In this case report, the bacteremia which appeared in a patient with pancreas cancer after ERCP was described.

Yoshida, T., N. Shiraki, et al. (2008). "Expression patterns of epiplakin1 in pancreas, pancreatic cancer and regenerating pancreas." Genes Cells **13**(7): 667-78.

Epiplakin1 (Eppk1) is a plakin family gene with its function remains largely unknown, although the plakin genes are known to function in interconnecting cytoskeletal filaments and anchoring them at plasma membrane-associated adhesive junction. Here we analyzed the expression patterns of Eppk1 in the developing and adult pancreas in the mice. In the embryonic pancreas, Eppk1+/Pdx1+ and Eppk1+/Sox9+ pancreatic progenitor cells were observed in early pancreatic epithelium. Since Pdx1

expression overlapped with that of Sox9 at this stage, these multipotent progenitor cells are Eppk1+/Pdx1+/Sox9+ cells. Then Eppk1 expression becomes confined to Ngn3+ or Sox9+ endocrine progenitor cells, and p48+ exocrine progenitor cells, and then restricted to the duct cells and a cells at birth. In the adult pancreas, Eppk1 is expressed in centroacinar cells (CACs) and in duct cells. Eppk1 is observed in pancreatic intraepithelial neoplasia (PanIN), previously identified as pancreatic ductal adenocarcinoma (PDAC) precursor lesions. In addition, the expansion of Eppk1-positive cells occurs in a caerulein-induced acute pancreatitis, an acinar cell regeneration model. Furthermore, in the partial pancreatectomy (Px) regeneration model using mice, Eppk1 is expressed in "ducts in foci", a tubular structure transiently induced. These results suggest that Eppk1 serves as a useful marker for detecting pancreatic progenitor cells in developing and regenerating pancreas.

Yoshikawa, A., S. Kuramoto, et al. (1998). "Peutz-Jeghers syndrome manifesting complete intussusception of the appendix and associated with a focal cancer of the duodenum and a cystadenocarcinoma of the pancreas: report of a case." Dis Colon Rectum **41**(4): 517-21.

The unusual occurrence of an "inside-out" appendix reported here is a case of complete intussusception of the appendix of a 45-year-old woman with Peutz-Jeghers syndrome in whom the diagnosis of intussusception was made preoperatively. At laparotomy, the lead point of intussusceptum was revealed to be a Peutz-Jeghers syndrome polyp of the appendix. There was also a cystic lesion in the pancreas, and subsequent distal pancreatectomy revealed a cystadenocarcinoma of the pancreas. Two jejunal Peutz-Jeghers syndrome polyps and two duodenal Peutz-Jeghers syndrome polyps were found via intraoperative endoscopies. The duodenal polyps were endoscopically removed, whereas a jejunal wedge resection was performed for the adjoining jejunal polyps. One of the two duodenal polyps possessed an adenocarcinoma focus. To our knowledge, this is the first report of complete intussusception of the appendix caused by a Peutz-Jeghers syndrome polyp.

Youmans, R., J. M. McGee, et al. (1996). "Surgical treatment of cancer of the pancreas in large community hospitals." J Okla State Med Assoc **89**(1): 16-21.

A retrospective study compares the success rates of surgical treatment of cancer of the pancreas in large community hospitals. Although none of the surgeons averaged as many as two pancreaticoduodenal resections per year for the period of this study, their results compared well with other published series except for a few centers and surgeons who did a very high volume of such resections. Results of the study indicate that well trained surgeons in well staffed and well equipped community hospitals can provide acceptable results in pancreaticoduodenectomies for cancer of the pancreas.

Yu, J., K. Ohuchida, et al. (2008). "LIM only 4 is overexpressed in late stage pancreas cancer." Mol Cancer **7**: 93.

BACKGROUND: LIM-only 4 (LMO4), a member of the LIM-only (LMO) subfamily of LIM domain-containing transcription factors, was initially reported to have an oncogenic role in breast cancer. We hypothesized that LMO4 may be related to pancreatic carcinogenesis as it is in breast carcinogenesis. If so, this could result in a better understanding of tumorigenesis in pancreatic cancer. METHODS: We measured LMO4 mRNA levels in cultured cells, pancreatic bulk tissues and microdissected target cells (normal ductal cells; pancreatic intraepithelial neoplasia-1B [PanIN-1B] cells; PanIN-2 cells; invasive ductal carcinoma [IDC] cells; intraductal papillary-mucinous adenoma [IPMA] cells; IPM borderline [IPMB] cells; and invasive and non-invasive IPM carcinoma [IPMC]) by quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR). RESULTS: 9 of 14 pancreatic cancer cell lines expressed higher levels of LMO4 mRNA than did the human pancreatic ductal epithelial cell line (HPDE). In bulk tissue samples, expression of LMO4 was higher in pancreatic carcinoma than in intraductal papillary-mucinous neoplasm (IPMN) or non-neoplastic pancreas ($p < 0.0001$ for both). We carried out microdissection-based analyses. IDC cells expressed significantly higher levels of LMO4 than did normal ductal epithelia or PanIN-1B cells ($p < 0.001$ for both) or PanIN-2 cells ($p = 0.014$). IPMC cells expressed significantly higher levels of LMO4 than did normal ductal epithelia ($p < 0.001$), IPMA ($p < 0.001$) and IPMB cells ($p = 0.003$). CONCLUSION: Pancreatic carcinomas (both IDC and IPMC) expressed significantly higher levels of LMO4 mRNA than did normal ductal epithelia, PanIN-1B, PanIN-2, IPMA and IPMB. These results suggested that LMO4 is overexpressed at late stages in carcinogenesis of pancreatic cancer.

Zemskov, V. S., O. L. Procopchuk, et al. (2000). "Ukrain (NSC-631570) in the treatment of pancreas cancer." Drugs Exp Clin Res **26**(5-6): 179-90.

The aim of this 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. Currently, there is no satisfactory treatment for pancreas cancer. The 12-month survival rate is approximately 18% for patients treated with gemcitabine and only around 2% for those treated with 5-fluorouracil. Between January 1, 1996 and December 31, 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. Other evaluation criteria included change in body weight, pain intensity (measured by analgesic consumption) and Kamofsky performance status. The one-year survival was 81% in the Ukrain group compared with 14% in the control group. The 2-year survival was 43% in the Ukrain group compared with 5% 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). The last follow-up of other patients was on September 6, 2000. Median survival was 17.17 months for Ukrain-treated patients and 6.97 months for the control group and mean survival was 21.86 and 8.92 months for the Ukrain and control groups, respectively ($p = 0.001$). Ukrain treatment was well tolerated. We conclude that Ukrain prolongs survival of pancreas cancer patients. To determine whether and to what extent this drug can be used as standard therapy in pancreas cancer, a phase III study should be carried out.

Zhao, H., D. Mandich, et al. (2007). "Expression of K homology domain containing protein overexpressed in cancer in pancreatic FNA for diagnosing adenocarcinoma of pancreas." Diagn Cytopathol **35**(11): 700-4.

We evaluated the immunocytochemical (ICC) expression of K homology domain containing protein overexpressed in cancer (KOC) in pancreatic endoscopic ultrasound-guided fine needle aspirates (EUS-FNAs) to assess its potential use as an adjunct in differentiating nonneoplastic (GI epithelium) and benign neoplastic epithelia (benign epithelial pancreatic neoplasms) from pancreatic adenocarcinoma cells. Forty-eight cases of EUS-FNAs with histological and/or clinical follow-up data were selected for this study. Alcohol-fixed and PAP-stained slides were stained with monoclonal antibody to KOC/L523S (clone 69.1). Results were recorded as negative or positive. KOC expression was present in 35/40 (88%) of adenocarcinomas (Ac) and was negative in all eight benign cases. The sensitivity and specificity were as follows: cytology 85 and 100%, KOC 88 and 100%; combination of cytology and KOC 95 and 100%. We conclude that KOC ICC expression on alcohol-fixed smears along with cytology improves the sensitivity of EUS-FNAs in the diagnosis of pancreatic Ac, and KOC reactivity is especially useful in differentiating Ac from nonneoplastic gastrointestinal epithelium and benign neoplastic epithelia.

Zittel, T. T., C. F. Mehl, et al. (2004). "Treatment of advanced rectal cancer in a patient after combined pancreas-kidney transplantation." Langenbecks Arch Surg **389**(1): 6-10.

BACKGROUND: Organ transplantation is a standard procedure today. Due to immunosuppressive drugs and increasing survival after organ transplantation, patients with transplanted organs carry an increased risk of developing malignant tumours. Accordingly, more patients with malignant tumours after transplantation will be faced by general or oncology surgeons. We report the case of a 48-year-old patient with advanced rectal cancer 6.5 years after pancreas-kidney-transplantation for type I diabetes. METHOD: The patient was treated with neo-adjuvant radio-chemotherapy, followed by low anterior rectal resection with total mesorectal excision. Consecutively, a solitary hepatic metastasis, a solitary pulmonary metastasis and a chest wall metastasis were resected over the course of 13 months. RESULT: The patient eventually died of metastasized cancer 32 months after therapy had been initiated, his organ grafts functioning well until his death. CONCLUSION: Our case report provides evidence that transplantation patients should receive standard oncology treatment, including neo-adjuvant treatment, so long as their general condition and organ graft functions allow us to do so, although a higher degree of morbidity might be encountered.

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6/24/2013