

## PANCREAS ALERTS

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*Am J Surg Pathol* 2008; Dec 15.  
(PMID: 19092633)

**Isolated solitary ducts (naked ducts) in adipose tissue: a specific but underappreciated finding of pancreatic adenocarcinoma and one of the potential reasons of understaging and high recurrence rate.**

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The distinction of ductal adenocarcinoma from chronic pancreatitis remains one of the most difficult challenges in surgical pathology. The glandular units of invasive carcinoma are often well formed with well-polarized cells, appearing deceptively benign. Conversely, the ducts of chronic pancreatitis may be atypical and pseudoinfiltrative as a result of acinar atrophy and fibrosis. The authors recently noted isolated solitary ductal units (ISDs) in adipose tissue to be a reliable indicator of adenocarcinoma. In this study, the frequency of ISDs was investigated in 105 pancreatic resections with ductal adenocarcinoma and 32 with chronic pancreatitis only. ISD was defined as a solitary gland lying individually in adipose tissue, either directly abutting adipocytes or separated from them by only a thin rim of fibromuscular tissue. ISD was detected in 50/105 (47.6%) of pancreatic resections for ductal adenocarcinoma, but not in any resections with chronic pancreatitis only (specificity 100%; sensitivity 47.6%). Most of the ISDs were very well differentiated and cytologically bland. A small subset of these units represented vascular invasion, in which the carcinoma cells epithelialized the vessel lining, transforming the vessel into a duct-like structure, virtually indistinguishable from normal ducts or PanINs. The vascular nature of these units was verified by Elastic-Van Gieson stain and muscular markers highlighting the elastic lamina and muscular wall, respectively. ISDs were often located in histologic sections taken for the evaluation of the retroperitoneal margin and pancreatic-free surfaces where adipose tissue is more abundant. In conclusion, ISD lying in adipose tissue unaccompanied by other elements, present in 47.6% of pancreatic resections when peripancreatic soft tissues away from the tumor are sampled, is a very specific finding for carcinoma that may be instrumental in the diagnosis and staging of carcinoma as well as margin evaluation.

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**Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: results of a prospective phase II trial.**

**Heinrich S, Schäfer M, Weber A, Hany TF, Bhure U, Pestalozzi BC, Clavien PA.**

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The authors aimed to evaluate the morbidity of pancreaticoduodenectomy after neoadjuvant chemotherapy for resectable pancreatic cancer and to assess its histologic and metabolic response. Adjuvant chemotherapy improves the outcome of pancreatic cancer, but 25% of patients remain unfit after surgery. Neoadjuvant chemotherapy can be offered to all patients in a multimodality approach, but its efficacy and surgical morbidity are unknown. Patients with resectable, cytologically proven adenocarcinoma of the pancreatic head received 4 bi-weekly cycles of gemcitabine (1,000 mg/m<sup>2</sup>) and cisplatin (50 mg/m<sup>2</sup>) in this prospective phase II trial. Staging and restaging included chest X-ray, abdominal computed tomography (CT), positron emission tomography (PET)/CT, endoscopic ultrasound, and laparoscopy. Fluorodeoxyglucose uptake was quantified by the standard-uptake value (SUV) on baseline and restaging PET/CT. Immunohistochemistry for GLUT-1 and Ki-67 was performed. The histologic response, cytopathic effects, and surgical complications were graded by respective scores. Twenty-four of 28 patients had resection for histologically confirmed adenocarcinoma. The surgical morbidity was low without perioperative death and one pancreatic fistula. Histologic response was documented in 54% and cytopathic effects in 83% of the patients. A significant SUV decrease occurred during chemotherapy (P=0.031), which correlated with the baseline SUV (P=0.001), Ki-67 expression (P=0.016), and histologic response (P=0.01). Neither the metabolic nor the histologic response was predictive of the median disease-free (9.2 months) or overall survival (26.5 months). In conclusion, neoadjuvant chemotherapy induced a significant metabolic and histologic response, which was best predicted by PET. Most importantly, surgery after neoadjuvant chemotherapy for pancreatic cancer was safe.

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**Determining pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-**

### **flurouracil-based chemoradiation therapy: effect of number of metastatic lymph nodes and lymph node ratio.**

**Asiyanbola B, Gleisner A, Herman JM, Choti MA, Wolfgang CL, Swartz M, et al.**

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There are limited data on patterns of recurrence and factors associated with local recurrence following pancreaticoduodenectomy for pancreatic adenocarcinoma and adjuvant 5-flurouracil-based chemoradiation therapy. Between 1995 and 2005, 905 patients underwent pancreaticoduodenectomy for pancreatic adenocarcinoma; 154 patients had complete pattern of recurrence data available. At median follow-up of 20.2 months, 103 (66.9%) patients recurred with median time to recurrence of 16.2 months. Most patients recurred with distant disease only (68.9%), while 21.4% patients recurred with local disease only; ten (9.7%) patients recurred with local and distant disease. Several factors were associated with local recurrence: poor tumor differentiation (hazard ratio, HR, 2.39) and presence of metastatic lymph nodes (HR 1.89, both  $P < 0.05$ ). Among N1 patients, poor tumor differentiation (HR 3.92),  $>5$  metastatic LN (HR 3.75), and lymph node ratio (LNR)  $>0.4$  (HR 2.96) had the highest risk of local recurrence (all  $P < 0.05$ ). Increasing LNR was associated with an incremental increased risk of local recurrence (LNR  $<0.2$ , 21.3%; LNR from 0.2 to 0.4, 25.2%; LNR  $>0.4$ , 40.4%;  $P < 0.05$ ). Although most patients who receive standard 5-flurouracil-based chemoradiation therapy will ultimately succumb to distant disease, about 30% recur locally. Poor tumor differentiation, a high number of metastatic LN ( $>5$ ), and LNR  $>0.4$  are associated with the highest risk of local failure. In these patients, radiation dose escalation and/or a combination of radiation with novel chemotherapeutic agents may be necessary to improve outcomes.

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### **Diagnosis of pancreatic adenocarcinoma using protein chip technology.**

**Liu D, Cao L, Yu J, Que R, Jiang W, Zhou Y, Zhu L.**

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The authors aimed to develop a serum-specific protein fingerprint which is capable of differentiating samples from patients with pancreatic cancer and those with other pancreatic conditions. The authors used SELDI-TOF-MS coupled with CM10 chips and bioinformatics tools to analyze a total of 118 serum samples in this study; 78 serum samples were analyzed to establish the

diagnostic models and the other 40 samples were analyzed on the second day as an independent test set. The analysis of this independent test set yielded a specificity of 91.6% and a sensitivity of 91.6% for pattern 1, which distinguished pancreatic adenocarcinoma (PC) from healthy individuals and a specificity of 80.0% and a sensitivity of 90.9% for pattern 2, which distinguished PC from chronic pancreatitis. In conclusion this study indicated that the SELDI-TOF-MS technique can facilitate the discovery of better serum tumor biomarkers and a combination of specific models is more accurate than a single model in diagnosis of PC.

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### **Proteomic analysis of pancreatic ductal adenocarcinoma compared with normal adjacent pancreatic tissue and pancreatic benign cystadenoma.**

**Cui Y, Tian M, Zong M, Teng M, Chen Y, Lu J, et al.**

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Dual expression of potential biomarkers in both benign and malignant pancreatic tumors was a major obstacle in the development of diagnostic biomarkers of early pancreatic cancer. To better understand the limitations of potential protein biomarkers in pancreatic cancer, the authors employed two-dimensional difference gel electrophoresis technology and tandem mass spectrometry to study protein expression profiles in pancreatic cancer tissues, benign pancreatic adenoma and normal adjacent pancreas. Seven differently expressed proteins were selected for validation by Western blot and/or immunohistochemistry. Twenty-one spots were overexpressed and 24 spots were downexpressed in pancreatic cancer compared with benign and normal adjacent tissues. This study demonstrated that three candidate pancreatic ductal adenocarcinoma biomarkers identified in previous studies, fructose-bisphosphate aldolase A, alpha-smooth muscle actin and vimentin, were also overexpressed in pancreatic cystadenoma, which might lower their further utility as biomarkers for pancreatic cancer. Aflatoxin B(1) aldehyde reductase (AKR7A2) was confirmed to be only highly expressed in pancreatic cancer, not in normal adjacent pancreas and benign tumors. In conclusion, the protein profile pattern of pancreatic cystadenoma was more similar to normal adjacent pancreas than pancreatic cancer. The authors identified panels of the upregulated proteins in pancreatic cancer, which have not been reported in prior proteomic studies. AKR7A2 may be a novel potential biomarker for pancreatic cancer.

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### **Histone H1x is highly expressed in human neuroendocrine cells and tumours.**

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Histone H1x is a ubiquitously expressed member of the H1 histone family. H1 histones, also called linker histones, stabilize compact, higher order structures of chromatin. In addition to their role as structural proteins, they actively regulate gene expression and participate in chromatin-based processes like DNA replication and repair. The epigenetic contribution of H1 histones to these mechanisms makes it conceivable that they also take part in malignant transformation. Based on results of a Blast data base search which revealed an accumulation of expressed sequence tags (ESTs) of H1x in libraries from neuroendocrine tumours (NETs), the authors evaluated the expression of H1x in NETs from lung and the gastrointestinal tract using immunohistochemistry. Relative protein and mRNA levels of H1x were analysed by Western blot analysis and quantitative real-time RT-PCR, respectively. Since several reports describe a change of the expression level of the replacement subtype H1.0 during tumorigenesis, the analysis of this subtype was included in this study. The authors found an increased expression of H1x but not of H1.0 in NET tissues in comparison to corresponding normal tissues. Even though the analysed NETs were heterogenous regarding their grade of malignancy, all except one showed a considerably higher protein amount of H1x compared with corresponding non-neoplastic tissue. Furthermore, double-labelling of H1x and chromogranin A in sections of pancreas and small intestine revealed that H1x is highly expressed in neuroendocrine cells of these tissues. The authors conclude that the high expression of histone H1x in NETs is probably due to the abundance of this protein in the cells from which these tumours originate.

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### **Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors.**

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Well-differentiated neuroendocrine tumors (WDNET) of the gastrointestinal tract, pancreas, and lung are histologically similar. Thus, predicting the site of origin of a metastasis is not possible on morphologic grounds. Prior immunohistochemical studies of WDNET have yielded conflicting results, and pancreatic and duodenal homeobox factor-1 (PDX-1) has not previously been evaluated in this context. The authors therefore analyzed the expression of CDX-2, PDX-1, TTF-1, and neuroendocrine secretory protein-55 (NESP-55), a recently described member of the chromogranin family, in primary and metastatic WDNET. In total, 64 gastrointestinal carcinoids (5 stomach; 5 duodenum; 31 ileum; 11 appendix; and 12 rectum); 39 pancreatic endocrine tumors (PET); and 20 pulmonary carcinoid tumors were studied. PET were positive for NESP-55 (16/39) and PDX-1 (11/39); 3/31 also showed heterogeneous positivity for CDX-2. Ileal carcinoids were exclusively positive for CDX-2 (30/31) and negative for all other markers. Appendiceal carcinoids were uniformly positive for CDX-2 (11/11). All rectal carcinoids were negative for CDX-2 and TTF-1; 2/12 were positive for PDX-1, and 1/12 for NESP-55. The gastric and duodenal carcinoids were only positive for PDX-1 (7/10). TTF-1 positivity was confined to pulmonary carcinoids (7/20); 1/20 was positive for NESP-55; and all were negative for CDX-2 and PDX-1. NESP-55 and PDX-1 positivity, in the presence of negative CDX-2 and TTF-1, was 97% specific for PET. The sensitivity and specificity of CDX-2 positivity for predicting an ileal primary, when PDX-1, NESP-55, and TTF-1 were negative, was 97% and 91%, respectively. TTF-1 positivity was confined to pulmonary carcinoids in the present study but was present in only about a third of cases. A panel of these 4 markers may be useful in predicting the primary site of metastatic WDNET.

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### **Chronic pancreatitis: report from a multicenter Italian survey (PanCroInfAISP) on 893 patients.**

**Frulloni L, Gabbriellini A, Pezzilli R, Zerbi A, Cavestro GM, Marotta F, et al.**

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No data on chronic pancreatitis in Italy are available yet. The aim of the study was to evaluate demographic, clinical, diagnostic and therapeutic aspects in patients suffering from chronic pancreatitis. Eligible patients were prospectively enrolled from 2000 to 2005. Information concerning demographic data, lifestyle risk factors, family and clinical history, associated factors (alcohol, autoimmunity, cystic

dystrophy of the duodenal wall, obstruction, genetic mutations) concomitant diseases, diagnostic findings, and pharmacological, endoscopic and surgical therapy were gathered. Eight hundred and 93 patients (74% males, mean age 53.7±15.2 years) were evaluated. 519/859 patients (60%) were drinkers and 555/840 (66%) were smokers. A strong positive correlation between drinking and cigarette consumption ( $r=0.53$ ;  $P<0.0001$ ) was found. Heavy alcohol consumption ( $>80$ g of alcohol/day for more than 5 years) was considered the most important risk factor in 300 patients (34%), obstruction in 238 (27%), alcohol and obstruction in 82 (9%), autoimmunity in 34 (4%), cystic dystrophy of the duodenal wall/groove pancreatitis in 55 (6%), gene mutations in 36 (4%), and none (idiopathic) in 148 (17%). Bile stones were diagnosed in 287 patients (33%) and cholecystectomy was performed in 329 patients (38%). Pancreatic calcifications were diagnosed in 547/879 patients (62%). Pancreatic surgery was performed in 273 patients (31%). Endoscopic sphincterotomy was performed in 371 patients (42%). Exocrine and endocrine insufficiency were found, respectively, in 373/834 (45%) and 275/885 patients (31%). In conclusion, an unexpected low frequency of alcohol abuse and new emerging associated risk factors for chronic pancreatitis were observed in Italy.

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### **Surgical versus nonsurgical management of pancreatic pseudocysts.**

**Johnson MD, Walsh RM, Henderson JM, Brown N, Ponsky J, Dumot J, et al.**

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The authors aimed to compare patient characteristics and outcome and also physician referral patterns between surgically and nonsurgically managed patients with pancreatic pseudocysts. Treatment of pancreatic pseudocysts can be accomplished by surgical, endoscopic, or percutaneous procedures. The ideal treatment method has not yet been defined. All patients treated for pancreatic pseudocyst between 1999 and 2005 were identified in the health services database. Patients were treated with surgical, endoscopic, and percutaneous drainage procedures at the discretion of the treating physician. Main outcome measures included complications, pseudocyst resolution, and treatment modality as a function of the treating physician's specialty. Thirty patients (49%) were treated surgically, 24 endoscopically (39%), and 7 (11%) with percutaneous drainage. The most common indications for treatment were symptoms of pain, and biliary or gastric outlet obstruction (81%). Patients

treated surgically and endoscopically were similar in terms of age (49 vs. 52 years), mean cyst diameter (9.1 vs. 9.5 cm,  $P=0.74$ ), incidence of chronic pancreatitis (50% vs. 32%,  $P=0.26$ ) and complicated pancreaticobiliary disease (69% vs. 60%). There were no differences in complications (20% vs. 21%) or pseudocyst resolution (93.3% vs. 87.5%,  $P=0.39$ ) between the surgical and endoscopic groups. There was no significant difference in the rate of surgical versus nonsurgical treatment in patients initially evaluated by surgeons versus nonsurgeons. In conclusion, surgical and endoscopic interventions for pancreatic pseudocysts are equally safe and effective with percutaneous drainage playing a less important role. Endoscopic drainage should be considered for initial therapy in appropriate patients.

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### **The role of redox status on chemokine expression in acute pancreatitis.**

**Yubero S, Ramudo L, Manso MA, De Dios I.**

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This study focused on the involvement of oxidative stress in the mechanisms mediating chemokine production in different cell sources during mild and severe acute pancreatitis (AP) induced by bile-pancreatic duct obstruction (BPDO) and 3.5% NaTc, respectively. N-acetylcysteine (NAC) was used as antioxidant treatment. Pancreatic glutathione depletion, acinar overexpression of monocyte chemoattractant protein-1 (MCP-1) and cytokine-induced neutrophil chemoattractant (CINC), and activation of p38MAPK, NF-kappaB and STAT3 were found in both AP models. NAC reduced the depletion of glutathione in BPDO- but not in NaTc-induced AP, in which oxidative stress overwhelmed the antioxidant capability of NAC. As a result, inhibition of the acinar chemokine expression and signalling pathways occurs in mild, but not in severe AP. However, MCP-1 and CINC expressions in whole pancreas and plasma chemokine levels were not reduced by NAC, even in BPDO-induced AP, suggesting that in addition to acini, other pancreatic cells produced chemokines by antioxidant resistant mechanisms. The high IL-6 plasma levels found during AP, both in NAC-treated and non-treated rats, pointed out cytokines as activating factors of chemokine expression in non-acinar cells. In conclusion, from early AP oxidant-mediated MAPK, NF-kappaB and STAT3 activation triggers the chemokine expression in acini but not in non-acinar cells.

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(PMID: 19110654)

### **Biliopancreatic reflux-pathophysiology and clinical implications.**

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The common bile duct and the main pancreatic duct open into the duodenum, where they frequently form a common channel. The sphincter of Oddi is located at the distal end of the pancreatic and bile ducts; it regulates the outflow of bile and pancreatic juice. In patients with a pancreaticobiliary maljunction, the action of the sphincter does not functionally affect the junction. Therefore, in these patients, two-way regurgitation (pancreatobiliary and biliopancreatic reflux) occurs. This results in various pathological conditions of the biliary tract and the pancreas. Biliopancreatic reflux could be confirmed by: operative or postoperative T-tube cholangiography; CT combined with drip infusion cholangiography; histological detection of gallbladder cancer cells in the main pancreatic duct; and reflux of bile on the cut surface of the pancreas. Biliopancreatic reflux occurs frequently in patients with a long common channel. Although the true prevalence, degree, and pathophysiology of biliopancreatic reflux remain unclear, biliopancreatic reflux is related to the occurrence of acute pancreatitis. Obstruction of a long common channel easily causes bile flow into the pancreas. Even if no obstruction is present, biliopancreatic reflux can still result in acute pancreatitis in some cases.

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### **Acute pancreatitis and the influence of socioeconomic deprivation.**

**Ellis MP, French JJ, Charnley RM.**

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A comprehensive epidemiological study of acute pancreatitis (AP) using reliable objective methods of patient identification with the inclusion of socioeconomic factors has not been reported previously. The study included all patients with AP identified by raised serum amylase or lipase levels admitted to 18 hospitals over 6 months. Clinical records were reviewed to confirm the diagnosis, aetiology and outcome. Patients were stratified into quintiles of socioeconomic deprivation. Age-standardized incidence (ASI) and mortality were calculated. Clinical data were reviewed for all 963 identified patients. The ASI was 56.5/100,000 per year, double the highest figure reported previously in the UK. Univariable logistic regression analysis showed a high ASI among older age groups (odds ratio, OR, 1.06 per year;  $P < 0.001$ ) and in areas of high deprivation (OR 2.40 between least and most deprived;  $P < 0.001$ ); the latter was predominantly related to alcoholic aetiology (OR 6.50; 95% confidence interval: 3.90 to 10.84). In conclusion, the incidence of AP based on a highly sensitive method of case identification was higher than previously reported. A clear relationship was found between socioeconomic deprivation and incidence of AP, which was largely explained by a higher incidence of alcoholic aetiology.

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